

Electronically Filed

PRELIMINARY AMENDMENT Under 37 CFR § 1.115 Address to: Mail Stop Patent Application Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450	Attorney Docket No.	REGN-024CON8
	Confirmation No.	To Be Assigned
	First Named Inventor	Furfine, Eric
	Application Number	To Be Assigned
	Filing Date	October 12, 2018
	Group Art Unit	
	Examiner Name	
	Title:	<i>“VEGF Antagonist Formulations Suitable for Intravitreal Administration”</i>

Sir:

Prior to the examination of the above-referenced application on the merits, please enter the amendments below.

AMENDMENTS TO THE CLAIMS

1. – 11. (Canceled)

12. (New) A vial comprising:

a vascular endothelial growth factor (VEGF) antagonist,

an organic co-solvent,

a buffer, and

a stabilizing agent,

wherein the VEGF antagonist is a fusion protein produced in a Chinese Hamster Ovary (CHO) cell, the fusion protein comprising an immunoglobulin-like (Ig) domain 2 of a first VEGF receptor and Ig domain 3 of a second VEGF receptor, and a multimerizing component.

13. (New) The vial of claim 12, wherein 90% or more of the weight of the fusion protein is not present as an aggregate.

14. (New) The vial of claim 12, wherein the first VEGF receptor is human Flt1 and the second VEGF receptor is selected from the group consisting of human Flk1 and the human Flt4.

15. (New) The vial of claim 14, wherein the fusion protein comprises an amino acid sequence of SEQ ID NO:4.

16. (New) The vial of claim 14, wherein the VEGF antagonist is a dimer of the fusion protein.

17. (New) The vial of claim 16, wherein the organic co-solvent is selected from the group consisting of polysorbate 20, polysorbate 90, polyethylene glycol (PEG), PEG3350, and propylene glycol.

18. (New) The vial of claim 17, wherein the stabilizing agent is selected from the group consisting of sucrose, sorbitol, glycerol, trehalose, and mannitol.

19. (New) The vial of claim 12, wherein the buffer comprises phosphate.

20. (New) The vial of claim 12, wherein the organic co-solvent is polysorbate 20, the buffer is phosphate, and the stabilizing agent is sucrose.

21. (New) A formulation comprising:

a vascular endothelial growth factor (VEGF) antagonist,

an organic co-solvent,

a buffer, and

a stabilizing agent,

wherein the VEGF antagonist is a fusion protein produced in a Chinese Hamster Ovary (CHO) cell, the fusion protein comprising an immunoglobulin-like (Ig) domain 2 of a first VEGF receptor and Ig domain 3 of a second VEGF receptor, and a multimerizing component.

22. (New) The formulation of claim 21, wherein 90% or more of the weight of the fusion protein is not present as an aggregate.

23. (New) The formulation of claim 21, wherein the first VEGF receptor is human Flt1 and the second VEGF receptor is selected from the group consisting of human Flk1 and the human Flt4.

24. (New) The formulation of claim 23, wherein the fusion protein comprises an amino acid sequence of SEQ ID NO:4.

25. (New) The formulation of claim 23, wherein the VEGF antagonist is a dimer of the fusion protein.

26. (New) The formulation of claim 25, wherein the organic co-solvent is selected for the group consisting of polysorbate 20, polysorbate 90, polyethylene glycol (PEG), PEG3350, and propylene glycol.

27. (New) The formulation of claim 26, wherein the stabilizing agent is selected from the group consisting of sucrose, sorbitol, glycerol, trehalose, and mannitol.

28. (New) The formulation of claim 21, wherein the buffer comprises phosphate.

29. (New) The formulation of claim 21, wherein the organic co-solvent is polysorbate 20, the buffer is phosphate, and the stabilizing agent is sucrose.

REMARKS UNDER 37 CFR § 1.115

Formal Matters

Claims 12-29 are pending after entry of the amendments set forth herein.

Claims 1-11 are canceled without prejudice.

New claims 12-29 are added. Support for these amendments is found in the originally filed now canceled claims 1-11 and the specification.

No new matter has been added.

PARENT APPLICATION

The parent application has been allowed. Further, as indicated above, correspondence and support for the current claims relative to those of the parent application can be reviewed and confirmed. In the event the Examiner has any questions with respect to claim support or other issues in connection with the application, the Examiner is respectfully requested to contact the undersigned attorney at the indicated telephone number to arrange for an interview to expedite this position of this application.

STATEMENT UNDER 37 C.F.R. §§1.56 AND 1.2

Applicants hereby advise the Examiner of the status of a co-pending application in compliance with the Applicant's duty to disclose under 37 C.F.R. §§1.56 and 1.2 (see also MPEP §2001.06(b)) as discussed in *McKesson Info. Soln. Inc., v. Bridge Medical Inc.*, 487 F.3d 897; 82 USPQ2d 1865 (Fed. Cir. 2007).

The Applicants wish to bring to the Examiner's attention U.S. Patent Application No. 11/818,463, filed June 14, 2007 which issued on October 27, 2009 as U.S. Patent 7,608,261.

The Applicants wish to bring to the Examiner's attention U.S. Patent Application No. 12/833,417, filed July 9, 2010 which issued on January 10, 2012 as U.S. Patent No. 8,092,803.

The Applicants wish to bring to the Examiner's attention U.S. Patent Application No. 13/329,770, filed December 19, 2011 which issued on July 9, 2013 as U.S. Patent No. 8,481,046.

The Applicants wish to bring to the Examiner's attention U.S. Patent Application No. 13/914,996, filed June 11, 2013 which issued on August 12, 2014 as U.S. Patent No. 8,802,107.

The Applicants wish to bring to the Examiner's attention U.S. Patent Application No. 14/330,096, filed July 14, 2014 which issued on May 17, 2016 as U.S. Patent No. 9,3340,594.

The Applicants wish to bring to the Examiner's attention U.S. Patent Application No. 15/095,606, filed April 11, 2016 which issued on March 13, 2018 as U.S. Patent No. 9,914,763.

The Applicants wish to bring to the Examiner's attention U.S. Patent Application No. 15/151/776, filed May 11, 2016 which issued on February 28, 2017 as U.S. Patent No. 9,580,489.

The Applicants wish to bring to the Examiner's attention U.S. Patent Application No. 15,879,294, filed January 24, 2018 for which no actions have been mailed.

These documents are available on PAIR, and thus are not provided with this communication. Please inform the undersigned if there is any difficulty in obtaining the documents from PAIR.

CONCLUSION

Applicant(s) submit(s) that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, please telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees up to a strict limit of \$3,000.00 beyond that authorized on the credit card, but not more than \$3,000.00 in additional fees due with any communication for the above referenced patent application, including but not limited to any necessary fees for extensions of time, or credit any overpayment of any amount to Deposit Account No. 50-0815, order number REGN-024CON8.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

Date: 12 October 2018

By: /Karl Bozicevic, Reg. No. 28,807/
Karl Bozicevic
Registration No. 28,807

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Application Data Sheet 37 CFR 1.76		Attorney Docket Number	REGN-024CON8
		Application Number	
Title of Invention	VEGF ANTAGONIST FORMULATIONS SUITABLE FOR INTRAVITREAL ADMINISTRATION		
The application data sheet is part of the provisional or nonprovisional application for which it is being submitted. The following form contains the bibliographic data arranged in a format specified by the United States Patent and Trademark Office as outlined in 37 CFR 1.76. This document may be completed electronically and submitted to the Office in electronic format using the Electronic Filing System (EFS) or the document may be printed and included in a paper filed application.			

Secrecy Order 37 CFR 5.2:

☐	Portions or all of the application associated with this Application Data Sheet may fall under a Secrecy Order pursuant to 37 CFR 5.2 (Paper filers only. Applications that fall under Secrecy Order may not be filed electronically.)
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Inventor Information:

Inventor 1				
Legal Name				
Prefix	Given Name	Middle Name	Family Name	Suffix
	Eric		FURFINE	
Residence Information (Select One) ☒ US Residency ☐ Non US Residency ☐ Active US Military Service				
City	Concord	State/Province	MA	Country of Residence ⁱ US
Mailing Address of Inventor:				
Address 1		315 Harrington Avenue		
Address 2				
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Postal Code	01742	Country ⁱ	US	
Inventor 2				
Legal Name				
Prefix	Given Name	Middle Name	Family Name	Suffix
	Daniel		DIX	
Residence Information (Select One) ☒ US Residency ☐ Non US Residency ☐ Active US Military Service				
City	LaGrangeville	State/Province	NY	Country of Residence ⁱ US
Mailing Address of Inventor:				
Address 1		55 Memory Trail		
Address 2				
City	LaGrangeville	State/Province	NY	
Postal Code	12540	Country ⁱ	US	
Inventor 3				
Legal Name				
Prefix	Given Name	Middle Name	Family Name	Suffix
	Kenneth		GRAHAM	

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Application Data Sheet 37 CFR 1.76		Attorney Docket Number	REGN-024CON8
		Application Number	
Title of Invention	VEGF ANTAGONIST FORMULATIONS SUITABLE FOR INTRAVITREAL ADMINISTRATION		

Residence Information (Select One)		☒ US Residency	☐ Non US Residency	☐ Active US Military Service
City	Pleasant Valley	State/Province	NY	Country of Residence ⁱ
US				

Mailing Address of Inventor:

Address 1	c/o Regeneron Pharmaceuticals, Inc.			
Address 2	777 Old Saw Mill River Road			
City	Tarrytown	State/Province	NY	
Postal Code	10591	Country ⁱ	US	

Inventor 4

Legal Name				
Prefix	Given Name	Middle Name	Family Name	Suffix
	Kelly		FRYE	

Residence Information (Select One)		☒ US Residency	☐ Non US Residency	☐ Active US Military Service
City	Mendham	State/Province	NJ	Country of Residence ⁱ
US				

Mailing Address of Inventor:

Address 1	3 McVickers Lane			
Address 2				
City	Mendham	State/Province	NJ	
Postal Code	07945	Country ⁱ	US	

All Inventors Must Be Listed - Additional Inventor Information blocks may be generated within this form by selecting the **Add** button.

Add

Correspondence Information:

Enter either Customer Number or complete the Correspondence Information section below.	
For further information see 37 CFR 1.33(a).	
☐ An Address is being provided for the correspondence information of this application.	
Customer Number	96387
Email Address	docket@bozpat.com
Add Email Remove Email	

Application Information:

Title of the Invention	VEGF ANTAGONIST FORMULATIONS SUITABLE FOR INTRAVITREAL ADMINISTRATION		
Attorney Docket Number	REGN-024CON8	Small Entity Status Claimed	☐
Application Type			
Subject Matter			
Total Number of Drawing Sheets (if any)	0	Suggested Figure for Publication (if any)	

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Application Data Sheet 37 CFR 1.76		Attorney Docket Number	REGN-024CON8
		Application Number	
Title of Invention	VEGF ANTAGONIST FORMULATIONS SUITABLE FOR INTRAVITREAL ADMINISTRATION		

Filing By Reference:

Only complete this section when filing an application by reference under 35 U.S.C. 111(c) and 37 CFR 1.57(a). Do not complete this section if application papers including a specification and any drawings are being filed. Any domestic benefit or foreign priority information must be provided in the appropriate section(s) below (i.e., "Domestic Benefit/National Stage Information" and "Foreign Priority Information").

For the purposes of a filing date under 37 CFR 1.53(b), the description and any drawings of the present application are replaced by this reference to the previously filed application, subject to conditions and requirements of 37 CFR 1.57(a).

Application number of the previously filed application	Filing date (YYYY-MM-DD)	Intellectual Property Authority or Country

Publication Information:

☐ Request Early Publication (Fee required at time of Request 37 CFR 1.219)

☐ **Request Not to Publish.** I hereby request that the attached application not be published under 35 U.S.C. 122(b) and certify that the invention disclosed in the attached application **has not and will not** be the subject of an application filed in another country, or under a multilateral international agreement, that requires publication at eighteen months after filing.

Representative Information:

Representative information should be provided for all practitioners having a power of attorney in the application. Providing this information in the Application Data Sheet does not constitute a power of attorney in the application (see 37 CFR 1.32). Either enter Customer Number or complete the Representative Name section below. If both sections are completed the customer Number will be used for the Representative Information during processing.

Please Select One:						☒ Customer Number	☐ US Patent Practitioner	☐ Limited Recognition (37 CFR 11.9)
Customer Number		96387						
Prefix	Given Name	Middle Name	Family Name	Suffix	Remove			
Registration Number								
Prefix	Given Name	Middle Name	Family Name	Suffix	Remove			
Registration Number								
Additional Representative Information blocks may be generated within this form by selecting the Add button.								

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Application Data Sheet 37 CFR 1.76		Attorney Docket Number	REGN-024CON8
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Title of Invention	VEGF ANTAGONIST FORMULATIONS SUITABLE FOR INTRAVITREAL ADMINISTRATION		

Domestic Benefit/National Stage Information:

This section allows for the applicant to either claim benefit under 35 U.S.C. 119(e), 120, 121, 365(c), or 386(c) or indicate National Stage entry from a PCT application. Providing benefit claim information in the Application Data Sheet constitutes the specific reference required by 35 U.S.C. 119(e) or 120, and 37 CFR 1.78.

When referring to the current application, please leave the "Application Number" field blank.

Prior Application Status	Pending	Remove	
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)
	Continuation of	15879294	2018-01-24

Prior Application Status	Patented	Remove			
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)	Patent Number	Issue Date (YYYY-MM-DD)
15879294	Continuation of	15095606	2016-04-11	9914763	2018-03-13

Prior Application Status	Patented	Remove			
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)	Patent Number	Issue Date (YYYY-MM-DD)
15095606	Continuation of	14330096	2014-07-14	9340594	2016-05-17

Prior Application Status	Patented	Remove			
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)	Patent Number	Issue Date (YYYY-MM-DD)
14330096	Continuation of	13914996	2013-06-11	8802107	2014-08-12

Prior Application Status	Patented	Remove			
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)	Patent Number	Issue Date (YYYY-MM-DD)
13914996	Continuation of	13329770	2011-12-19	8481046	2013-07-09

Prior Application Status	Patented	Remove			
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)	Patent Number	Issue Date (YYYY-MM-DD)
13329770	Continuation of	12833417	2010-07-09	8092803	2012-01-10

Prior Application Status	Patented	Remove			
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)	Patent Number	Issue Date (YYYY-MM-DD)
12833417	Continuation of	12560885	2009-09-16	7807164	2010-10-05

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		Application Number	
Title of Invention	VEGF ANTAGONIST FORMULATIONS SUITABLE FOR INTRAVITREAL ADMINISTRATION		

Prior Application Status		Patented	Remove		
Application Number	Continuity Type	Prior Application Number	Filing Date (YYYY-MM-DD)	Patent Number	Issue Date (YYYY-MM-DD)
12560885	Division of	11818463	2007-06-14	7608261	2009-10-27

Prior Application Status		Expired	Remove	
Application Number	Continuity Type	Prior Application Number	Filing or 371(c) Date (YYYY-MM-DD)	
11818463	Claims benefit of provisional	60814484	2006-06-16	

Additional Domestic Benefit/National Stage Data may be generated within this form by selecting the **Add** button.

Foreign Priority Information:

This section allows for the applicant to claim priority to a foreign application. Providing this information in the application data sheet constitutes the claim for priority as required by 35 U.S.C. 119(b) and 37 CFR 1.55. When priority is claimed to a foreign application that is eligible for retrieval under the priority document exchange program (PDX) the information will be used by the Office to automatically attempt retrieval pursuant to 37 CFR 1.55(i)(1) and (2). Under the PDX program, applicant bears the ultimate responsibility for ensuring that a copy of the foreign application is received by the Office from the participating foreign intellectual property office, or a certified copy of the foreign priority application is filed, within the time period specified in 37 CFR 1.55(g)(1).

Application Number	Country ⁱ	Filing Date (YYYY-MM-DD)	Access Code ⁱ (if applicable)

Additional Foreign Priority Data may be generated within this form by selecting the **Add** button.

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications

This application (1) claims priority to or the benefit of an application filed before March 16, 2013 and (2) also contains, or contained at any time, a claim to a claimed invention that has an effective filing date on or after March 16, 2013.

☐ NOTE: By providing this statement under 37 CFR 1.55 or 1.78, this application, with a filing date on or after March 16, 2013, will be examined under the first inventor to file provisions of the AIA.

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Application Data Sheet 37 CFR 1.76	Attorney Docket Number	REGN-024CON8
	Application Number	
Title of Invention	VEGF ANTAGONIST FORMULATIONS SUITABLE FOR INTRAVITREAL ADMINISTRATION	

Authorization or Opt-Out of Authorization to Permit Access:

When this Application Data Sheet is properly signed and filed with the application, applicant has provided written authority to permit a participating foreign intellectual property (IP) office access to the instant application-as-filed (see paragraph A in subsection 1 below) and the European Patent Office (EPO) access to any search results from the instant application (see paragraph B in subsection 1 below).

Should applicant choose not to provide an authorization identified in subsection 1 below, applicant **must opt-out** of the authorization by checking the corresponding box A or B or both in subsection 2 below.

NOTE: This section of the Application Data Sheet is **ONLY** reviewed and processed with the **INITIAL** filing of an application. After the initial filing of an application, an Application Data Sheet cannot be used to provide or rescind authorization for access by a foreign IP office(s). Instead, Form PTO/SB/39 or PTO/SB/69 must be used as appropriate.

1. Authorization to Permit Access by a Foreign Intellectual Property Office(s)

A. Priority Document Exchange (PDX) - Unless box A in subsection 2 (opt-out of authorization) is checked, the undersigned hereby **grants the USPTO authority** to provide the European Patent Office (EPO), the Japan Patent Office (JPO), the Korean Intellectual Property Office (KIPO), the State Intellectual Property Office of the People's Republic of China (SIPO), the World Intellectual Property Organization (WIPO), and any other foreign intellectual property office participating with the USPTO in a bilateral or multilateral priority document exchange agreement in which a foreign application claiming priority to the instant patent application is filed, access to: (1) the instant patent application-as-filed and its related bibliographic data, (2) any foreign or domestic application to which priority or benefit is claimed by the instant application and its related bibliographic data, and (3) the date of filing of this Authorization. See 37 CFR 1.14(h)(1).

B. Search Results from U.S. Application to EPO - Unless box B in subsection 2 (opt-out of authorization) is checked, the undersigned hereby **grants the USPTO authority** to provide the EPO access to the bibliographic data and search results from the instant patent application when a European patent application claiming priority to the instant patent application is filed. See 37 CFR 1.14(h)(2).

The applicant is reminded that the EPO's Rule 141(1) EPC (European Patent Convention) requires applicants to submit a copy of search results from the instant application without delay in a European patent application that claims priority to the instant application.

2. Opt-Out of Authorizations to Permit Access by a Foreign Intellectual Property Office(s)

- ☐ A. Applicant **DOES NOT** authorize the USPTO to permit a participating foreign IP office access to the instant application-as-filed. If this box is checked, the USPTO will not be providing a participating foreign IP office with any documents and information identified in subsection 1A above.
- ☐ B. Applicant **DOES NOT** authorize the USPTO to transmit to the EPO any search results from the instant patent application. If this box is checked, the USPTO will not be providing the EPO with search results from the instant application.

NOTE: Once the application has published or is otherwise publicly available, the USPTO may provide access to the application in accordance with 37 CFR 1.14.

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	REGN-024CON8
		Application Number	
Title of Invention	VEGF ANTAGONIST FORMULATIONS SUITABLE FOR INTRAVITREAL ADMINISTRATION		

Applicant Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

Applicant 1

If the applicant is the inventor (or the remaining joint inventor or inventors under 37 CFR 1.45), this section should not be completed. The information to be provided in this section is the name and address of the legal representative who is the applicant under 37 CFR 1.43; or the name and address of the assignee, person to whom the inventor is under an obligation to assign the invention, or person who otherwise shows sufficient proprietary interest in the matter who is the applicant under 37 CFR 1.46. If the applicant is an applicant under 37 CFR 1.46 (assignee, person to whom the inventor is obligated to assign, or person who otherwise shows sufficient proprietary interest) together with one or more joint inventors, then the joint inventor or inventors who are also the applicant should be identified in this section.

[Clear](#)

☐ Assignee
☐ Legal Representative under 35 U.S.C. 117
☐ Joint Inventor

☒ Person to whom the inventor is obligated to assign.
☐ Person who shows sufficient proprietary interest

If applicant is the legal representative, indicate the authority to file the patent application, the inventor is:

Name of the Deceased or Legally Incapacitated Inventor:

If the Applicant is an Organization check here. ☒

Organization Name REGENERON PHARMACEUTICALS, INC.

Mailing Address Information For Applicant:

Address 1	777 Old Saw Mill River Road		
Address 2			
City	Tarrytown	State/Province	NY
Country ⁱ	US	Postal Code	10591
Phone Number		Fax Number	
Email Address			

Additional Applicant Data may be generated within this form by selecting the Add button.

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	REGN-024CON8
		Application Number	
Title of Invention	VEGF ANTAGONIST FORMULATIONS SUITABLE FOR INTRAVITREAL ADMINISTRATION		

Assignee Information including Non-Applicant Assignee Information:

Providing assignment information in this section does not substitute for compliance with any requirement of part 3 of Title 37 of CFR to have an assignment recorded by the Office.

Assignee 1						
Complete this section if assignee information, including non-applicant assignee information, is desired to be included on the patent application publication. An assignee-applicant identified in the "Applicant Information" section will appear on the patent application publication as an applicant. For an assignee-applicant, complete this section only if identification as an assignee is also desired on the patent application publication.						
If the Assignee or Non-Applicant Assignee is an Organization check here.			☒			
Organization Name	REGENERON PHARMACEUTICALS, INC.					
Mailing Address Information For Assignee including Non-Applicant Assignee:						
Address 1		777 Old Saw Mill River Road				
Address 2						
City	Tarrytown	State/Province	NY			
Country i	US	Postal Code	10591			
Phone Number		Fax Number				
Email Address						
Additional Assignee or Non-Applicant Assignee Data may be generated within this form by selecting the Add button.						

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it contains a valid OMB control number.

Application Data Sheet 37 CFR 1.76		Attorney Docket Number	REGN-024CON8
		Application Number	
Title of Invention	VEGF ANTAGONIST FORMULATIONS SUITABLE FOR INTRAVITREAL ADMINISTRATION		

Signature:

NOTE: This Application Data Sheet must be signed in accordance with 37 CFR 1.33(b). **However, if this Application Data Sheet is submitted with the INITIAL filing of the application and either box A or B is not checked in subsection 2 of the "Authorization or Opt-Out of Authorization to Permit Access" section, then this form must also be signed in accordance with 37 CFR 1.14(c).**

This Application Data Sheet **must** be signed by a patent practitioner if one or more of the applicants is a **juristic entity** (e.g., corporation or association). If the applicant is two or more joint inventors, this form must be signed by a patent practitioner, **all** joint inventors who are the applicant, or one or more joint inventor-applicants who have been given power of attorney (e.g., see USPTO Form PTO/AIA/81) on behalf of **all** joint inventor-applicants.

See 37 CFR 1.4(d) for the manner of making signatures and certifications.

Signature	/Karl Boziceivc/			Date (YYYY-MM-DD)	
First Name	Karl	Last Name	Bozicevic	Registration Number	28807
Additional Signature may be generated within this form by selecting the Add button.					

Electronic Patent Application Fee Transmittal				
Application Number:				
Filing Date:				
Title of Invention:		VEGF ANTAGONIST FORMULATIONS SUITABLE FOR INTRAVITREAL ADMINISTRATION		
First Named Inventor/Applicant Name:		Eric FURFINE		
Filer:		Karl Bozicevic		
Attorney Docket Number:		REGN-024CON8		
Filed as Large Entity				
Filing Fees for Utility under 35 USC 111(a)				
Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
Basic Filing:				
UTILITY APPLICATION FILING	1011	1	300	300
UTILITY SEARCH FEE	1111	1	660	660
UTILITY EXAMINATION FEE	1311	1	760	760
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Miscellaneous:				
Total in USD (\$)				1720

Electronic Acknowledgement Receipt

EFS ID:	33998938
Application Number:	16159269
International Application Number:	
Confirmation Number:	5813
Title of Invention:	VEGF ANTAGONIST FORMULATIONS SUITABLE FOR INTRAVITREAL ADMINISTRATION
First Named Inventor/Applicant Name:	Eric FURFINE
Customer Number:	96387
Filer:	Karl Bozicevic
Filer Authorized By:	
Attorney Docket Number:	REGN-024CON8
Receipt Date:	12-OCT-2018
Filing Date:	
Time Stamp:	17:06:49
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	CARD
Payment was successfully received in RAM	\$ 1720
RAM confirmation Number	101518INTEFSW17075200
Deposit Account	
Authorized User	

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

File Listing:					
Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		REGN-024CON8_appln_as fld. pdf	766509	yes	16
			8daf0d517068c168f5c827e98848eb344ea0df38		
	Multipart Description/PDF files in .zip description				
	Document Description		Start	End	
	Specification		1	14	
	Claims		15	15	
	Abstract		16	16	
Warnings:					
Information:					
2	Oath or Declaration filed	REGN-024CON8_declaration. pdf	551390	no	4
			8a857f03087a869974574de3cf74617f361f334f		
Warnings:					
Information:					
3	Sequence Listing	REGN-024CON8_2018-10-12_s eq_list_trans.pdf	27112	no	1
			01b1c78ea69b9259a7f9454f850cde27b2c29e09		
Warnings:					
Information:					
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	Multipart Description/PDF files in .zip description				
	Document Description		Start	End	
	Preliminary Amendment		1	1	
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	Applicant Arguments/Remarks Made in an Amendment		5	6	
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6	Application Data Sheet	WebADS.pdf	175393	no	9
			4fa3fff81280db784a8bfd08528e973e6447a faa		
Warnings:					
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7	Fee Worksheet (SB06)	fee-info.pdf	34839	no	2
			3e38015eb30711a7e40f4085d91f2ba46c4 7da4b		
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VEGF ANTAGONIST FORMULATIONS SUITABLE FOR INTRAVITREAL ADMINISTRATION

Cross-Reference to Related Applications

[0001] This application is a continuation application of U.S. patent application Ser. No. 14/330,096, filed July 14, 2014, which is a continuation of U.S. patent application Ser. No. 13/914,996, filed Jun. 11, 2013, which issued as U.S. Pat. No. 8,802,107 on Aug. 12, 2014, which is a continuation application of U.S. patent application Ser. No. 13/329,770, filed Dec. 19, 2011, which issued as U.S. Pat. No. 8,481,046 on Jul. 9, 2013, which is a continuation application of U.S. patent application Ser. No. 12/833,417, filed Jul. 9, 2010, which issued as U.S. Pat. No. 8,092,803 on Jan. 10, 2012, which is a continuation application of U.S. patent application Ser. No. 12/560,885, filed Sep. 16, 2009, which issued as U.S. Pat. No. 7,807,164 on Oct. 5, 2010, which is a divisional application of U.S. patent application Ser. No. 11/818,463, filed Jun. 14, 2007, which issued as U.S. Pat. No. 7,608,261 on Oct. 27, 2009, which claims the benefit under 35 U.S.C. § 119(e) of U.S. Provisional Application No. 60/814,484, filed 16 Jun. 2006, which applications are each hereby incorporated by reference.

BACKGROUND OF INVENTION

Field of the Invention

[0002] The present invention is directed to pharmaceutical formulations suitable for intravitreal administration comprising agents capable of inhibiting vascular endothelial growth factor (VEGF), and to methods for making and using such formulations. The invention includes liquid pharmaceutical formulations having increased stability, as well as formulations that may be lyophilize and reconstituted for intravitreal administration.

Statement of Related Art

[0003] Vascular endothelial growth factor (VEGF) expression is nearly ubiquitous in human cancer, consistent with its role as a key mediator of tumor neoangiogenesis. Blockade of VEGF function, by binding to the molecule or its VEGFR-2 receptor, inhibits growth of implanted tumor cells in multiple different xenograft models (see, for example, Gerber et al. (2000) Cancer Res. 60:6253-6258). A soluble VEGF-specific fusion protein antagonist, termed a “VEGF trap” has been described (Kim et al. (2002) Proc. Natl. Acad. Sci. USA 99:11399-404; Holash et al. (2002) Proc.

Natl. Acad. Sci. USA 99:11393-8), which applications are specifically incorporated by reference in their entirety.

[0004] Ophthalmic formulations are known, see for example, U.S. 7,033,604 and 6,777,429. An ophthalmic formulation of a VEGF antibody is described in US 6,676,941.

[0005] Lyophilization (freeze drying under controlled conditions) is commonly used for long-term storage of proteins. The lyophilized protein is substantially resistant to degradation, aggregation, oxidation, and other degenerative processes while in the freeze-dried state (see, for example, U.S. 6,436,897).

BRIEF SUMMARY OF THE INVENTION

[0006] Stable formulations of a VEGF-specific fusion protein antagonist are provided.

Pharmaceutically acceptable formulations are provided that comprise a VEGF “trap” antagonist with a pharmaceutically acceptable carrier. In specific embodiments, liquid and lyophilized formulations are provided.

[0007] In a first aspect, a stable liquid ophthalmic formulation of a VEGF-specific fusion protein antagonist is provided, comprising a fusion protein that comprises a receptor component consisting essentially of an immunoglobulin-like (Ig) domain 2 of a first VEGF receptor and Ig domain 3 of a second VEGF receptor, and a multimerizing component (also termed a “VEGF trap”). In a specific embodiment of the VEGF-specific fusion protein antagonist, the first VEGF receptor is Flt1 and the second VEGF receptor is Flk1 or Flt4. In a more specific embodiment the fusion protein has the amino acid sequence of SEQ ID NO:2 or SEQ ID NO:4. Preferably, the VEGF antagonist is a dimer comprising two fusion proteins of SEQ ID NO:4.

[0008] In one aspect, a stable liquid ophthalmic formulation is provided that comprises 1-100 mg/ml VEGF-specific fusion protein antagonist, 0.01-5% of one or more organic co-solvent(s), 30-150 mM of one or more tonicity agent(s), 5-40 mM of a buffering agent, and optionally, 1.0-7.5% of a stabilizing agent, pH between about 5.8-7.0.

[0009] In one or more specific embodiments, the organic co-solvent may be polysorbate, for example, polysorbate 20 or polysorbate 80, polyethylene glycol (PEG), for example, PEG 3350, or propylene glycol, or a combination thereof; the tonicity agent may be, for example, sodium chloride or potassium chloride; the stabilizing agent may be sucrose, sorbitol, glycerol, trehalose, or mannitol; and the buffering agent may be, for example, phosphate buffer. In a specific embodiment,

the phosphate buffer is a sodium phosphate buffer.

[0010] In various embodiments, the organic co-solvent is polysorbate and/or PEG, the stabilizing agent is sucrose, the buffering agent is phosphate buffer, and the tonicity agent is sodium chloride.

[0011] More specifically, the stable liquid ophthalmic formulation comprises about 40-50 mg/ml of the VEGF antagonist (SEQ ID NO:4), about 10 mM phosphate buffer, 0.01-3% polysorbate and/or PEG, 40-135 mM sodium chloride, and optionally 5.0% sucrose, pH about 6.2-6.3.

[0012] In a specific preferred embodiment, the stable liquid ophthalmic formulation comprises about 50 mg/ml of the VEGF antagonist (SEQ ID NO:4), 10 mM sodium phosphate buffer, 50 mM sodium chloride, 0.1% polysorbate, and 5% sucrose, pH about 6.2-6.3.

[0013] In a specific preferred embodiment, the stable liquid ophthalmic formulation comprises about 50 mg/ml of the VEGF antagonist (SEQ ID NO:4), 10 mM sodium phosphate buffer, 50 mM sodium chloride, 3% PEG, and 5% sucrose, pH about 6.2-6.3.

[0014] In a specific preferred embodiment, the stable liquid ophthalmic formulation comprises about 40 mg/ml of the VEGF antagonist (SEQ ID NO:4), 10 mM sodium phosphate buffer, 40 mM sodium chloride, 0.03% polysorbate, and 5% sucrose, pH about 6.2-6.3.

[0015] In a specific preferred embodiment, the stable liquid ophthalmic formulation comprises about 40 mg/ml of the VEGF antagonist (SEQ ID NO:4), 10 mM sodium phosphate buffer, 135 mM sodium chloride, and 0.03% polysorbate, pH about 6.2-6.3.

[0016] In another aspect, a stable liquid ophthalmic formulation is provided that comprises 1-100 mg/ml VEGF-specific fusion protein antagonist; 0.01-5% of one or more organic co-solvent(s); 5-40 mM of a buffering agent; and optionally 30-150 mM of one or more tonicity agent(s) and/or 1.0-7.5% of a stabilizing agent; having a pH between about 5.8-7.0.

[0017] In various embodiments, the VEGF antagonist (SEQ ID NO:4) is present at a concentration of about 10 to about 80 mg/ml. In various embodiments, the VEGF antagonist (SEQ ID NO:4) is present at a concentration of about 10, about 20, about 30, about 40, about 50, about 60, about 70, or about 80 mg/ml. In a preferred embodiment, the VEGF antagonist (SEQ ID NO:4) is present at a concentration of about 40 mg/ml.

[0018] In another embodiment, the stabilizing agent is selected from one or more of sucrose, sorbitol, glycerol, trehalose, and mannitol.

[0019] In another embodiment, the organic co-solvent is selected from one or more of polysorbate, for example, polysorbate 20 or polysorbate 80, polyethylene glycol (PEG), for example, PEG 3350, and propylene glycol.

[0020] In another embodiment, the buffer is a phosphate buffer, for example, sodium phosphate.

[0021] In another embodiment, the tonicity agent is a salt, for example, sodium chloride.

[0022] In one embodiment, the stable liquid ophthalmic formulation comprises 10 mM sodium phosphate buffer, about 0.03 to about 0.1% polysorbate and/or about 3% PEG or propylene glycol, about 40 mM sodium chloride, and about 5% sucrose. In a specific embodiment, the stable liquid ophthalmic formulation comprises 10 mM sodium phosphate buffer, about 0.03% polysorbate, about 40 mM sodium chloride, and about 5% sucrose. In another specific embodiment, the pH of the formulation is about 6.2 to about 6.3. In another specific embodiment, the pH is achieved by mixing mono- and dibasic sodium phosphate to the desired pH without acid/base titration.

[0023] In a specific embodiment, the stable liquid ophthalmic formulation consists essentially of a VEGF antagonist (SEQ ID NO:4) at 40 mg/ml, 10 mM sodium phosphate buffer, polysorbate at 0.03%, sodium chloride at 40 mM, and sucrose at 5%, pH 6.2-6.3.

[0024] In another aspect, a stable liquid ophthalmic formulation is provided that comprises about 10 to about 80 mg/ml VEGF antagonist, about 10 mM sodium phosphate buffer, about 0.03% polysorbate, and about 135 mM sodium chloride, pH 6.2 to 6.3.

[0025] In various embodiments, the VEGF antagonist (SEQ ID NO:4) is present at a concentration of about 10 to about 80 mg/ml. In various embodiments, the VEGF antagonist (SEQ ID NO:4) is present at a concentration of about 10, about 20, about 30, about 40, about 50, about 60, about 70, or about 80 mg/ml. In a specific embodiment, the VEGF antagonist (SEQ ID NO:4) is present at a concentration of about 40 mg/ml.

[0026] In one embodiment, the stable liquid ophthalmic formulation comprises 40 mg/ml of VEGF antagonist (SEQ ID NO:4), 10 mM sodium phosphate buffer, 0.03% polysorbate, and 135 mM sodium chloride at pH 6.2-6.3. In a specific embodiment, the stable liquid ophthalmic formulation consists essentially of 40 mg/ml of VEGF antagonist (SEQ ID NO:4), 10 mM sodium phosphate buffer, 0.03% polysorbate, and 135 mM sodium chloride at pH 6.2-6.3.

[0027] In another aspect, a lyophilizable formulation of a VEGF antagonist is provided, wherein upon lyophilization followed by reconstitution, a stable liquid ophthalmic formulation as described

herein is obtained.

[0028] In another aspect, a lyophilizable formulation of a vascular endothelial growth factor (VEGF)-specific fusion protein antagonist is provided, comprising 5-50 mg/ml of the VEGF antagonist, 5-25 mM buffer, such as phosphate buffer, 0.01 to 0.15% of one or more of an organic co-solvent, such as polysorbate, propylene glycol and/or PEG, and optionally 1-10% of a stabilizing agent such as sucrose, sorbitol, trehalose, glycerol, or mannitol, pH about 5.8-7.0. In various embodiments, the VEGF antagonist (SEQ ID NO:4) is present at about 5, about 10, about 20, about 30, or about 40 mg/ml. In a specific embodiment, the lyophilizable ophthalmic formulation of the invention comprises 20 mg/ml of the VEGF antagonist, 10 mM sodium phosphate buffer, 0.03% polysorbate, 0.1% PEG, and 2.5% sucrose, pH about 6.2-6.3. In further embodiments, the lyophilizable formulation further comprises sodium chloride. In a specific embodiment, the sodium chloride is present at a concentration of about 20 mM. In another specific embodiment, the sodium chloride is present at a concentration of about 67.5 mM.

[0029] In another specific embodiment, the lyophilizable ophthalmic formulation of the invention comprises 20 mg/ml of the VEGF antagonist, 5 mM sodium phosphate buffer, 0.015% polysorbate, 20 mM sodium chloride, and 2.5% sucrose, pH about 6.2-6.3.

[0030] In another embodiment, the lyophilizable ophthalmic formulation comprises 5 mg/ml, 10 mg/ml, or 40 mg/ml VEGF antagonist, 5 mM sodium phosphate buffer, 0.015% polysorbate, 20 mM sodium chloride, and 2.5% sucrose, at pH 6.2-6.3. In a specific embodiment, the lyophilizable ophthalmic formulation consists essentially of 5 mg/ml, 10 mg/ml, or 40 mg/ml VEGF antagonist (SEQ ID NO:4), 5 mM sodium phosphate buffer, 0.015% polysorbate, 20 mM sodium chloride, and 2.5% sucrose, at pH 6.2-6.3.

[0031] In another specific embodiment, the lyophilizable ophthalmic formulation comprises 20 mg/ml of the VEGF antagonist, 5 mM sodium phosphate buffer, 0.015% polysorbate, and 67.5 mM sodium chloride, pH about 6.2-6.3. In a more specific embodiment, the lyophilizable ophthalmic formulation consists essentially of 20 mg/ml of the VEGF antagonist (SEQ ID NO:4), 5 mM sodium phosphate buffer, 0.015% polysorbate, and 67.5 mM sodium chloride, pH 6.2-6.3.

[0032] In another specific embodiment, the lyophilizable ophthalmic formulation comprises 5 mg/ml, 10 mg/ml, or 40 mg/ml VEGF antagonist, 5 mM sodium phosphate buffer, 0.015% polysorbate, and 67.5 mM sodium chloride, pH about 6.2-6.3. In a more specific embodiment, the lyophilizable ophthalmic formulation consists essentially of 5 mg/ml, 10 mg/ml, or 40 mg/ml VEGF

antagonist (SEQ ID NO:4), 5 mM sodium phosphate buffer, 0.015% polysorbate, and 67.5 mM sodium chloride, pH about 6.2-6.3.

[0033] Generally, the reconstituted formulation is about 2 times the concentration of the pre-lyophilized formulation, e.g., a 20 mg fusion protein/ml pre-lyophilized formulation is reconstituted to a final formulation of 40 mg fusion protein/ml.

[0034] Generally, the lyophilized formulation is reconstituted with sterile water suitable for injection. In one embodiment, the reconstitution liquid is bacteriostatic water.

[0035] In another aspect, the invention features a method of producing a lyophilized formulation of a VEGF-specific fusion protein antagonist, comprising subjecting the lyophilizable formulation of the invention to lyophilization to generate a lyophilized formulation. The lyophilized formulation may be lyophilized by any method known in the art for lyophilizing a liquid.

[0036] In another related aspect, the invention features a method of producing a reconstituted lyophilized formulation of a VEGF antagonist, comprising reconstituting the lyophilized formulation of the invention to a reconstituted formulation. In one embodiment, the reconstituted formulation is twice the concentration of the pre-lyophilized formulation, e.g., the method of the invention comprises: (a) producing a pre-lyophilized formulation of a VEGF-specific fusion protein antagonist, (b) subjecting the pre-lyophilized formulation of step (a) to lyophilization; and (c) reconstituting the lyophilized formulation of step (b).

[0037] The invention further features ophthalmic formulations provided in a pre-filled syringe or vial, particularly suitable for intravitreal administration.

[0038] Other objects and advantages will become apparent from a review of the ensuing detailed description.

DETAILED DESCRIPTION OF THE INVENTION

[0039] The present invention is not limited to particular methods, and experimental conditions described, as such methods and conditions may vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to be limiting unless indicated, since the scope of the present invention will be limited only by the appended claims.

[0040] Unless stated otherwise, all technical and scientific terms and phrases used herein have the same meaning as commonly understood by one of ordinary skill in the art to which the invention belongs. Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, the preferred methods and materials are now described. All publications mentioned herein are incorporated herein by reference.

General Description

[0041] Safe handling and administration of formulations comprising proteins represent significant challenges to pharmaceutical formulators. Proteins possess unique chemical and physical properties that present stability problems: a variety of degradation pathways exist for proteins, implicating both chemical and physical instability. Chemical instability includes deamination, aggregation, clipping of the peptide backbone, and oxidation of methionine residues. Physical instability encompasses many phenomena, including, for example, aggregation and/or precipitation.

[0042] Chemical and physical stability can be promoted by removing water from the protein. Lyophilization (freeze-drying under controlled conditions) is commonly used for long-term storage of proteins. The lyophilized protein is substantially resistant to degradation, aggregation, oxidation, and other degenerative processes while in the freeze-dried state. The lyophilized protein may be reconstituted with water optionally containing a bacteriostatic preservative (e.g., benzyl alcohol) prior to administration.

Definitions

[0043] The term “carrier” includes a diluent, adjuvant, excipient, or vehicle with which a composition is administered. Carriers can include sterile liquids, such as, for example, water and oils, including oils of petroleum, animal, vegetable or synthetic origin, such as, for example, peanut oil, soybean oil, mineral oil, sesame oil and the like.

[0044] The term “excipient” includes a non-therapeutic agent added to a pharmaceutical composition to provide a desired consistency or stabilizing effect. Suitable pharmaceutical excipients include, for example, starch, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, sodium stearate, glycerol monostearate, talc, sodium chloride, dried skim milk, glycerol, propylene, glycol, water, ethanol and the like.

[0045] The term “lyophilized” or “freeze-dried” includes a state of a substance that has been subjected to a drying procedure such as lyophilization, where at least 90% of moisture has been

removed.

VEGF Antagonists

[0046] A VEGF antagonist is a compound capable of blocking or inhibiting the biological action of vascular endothelial growth factor (VEGF), and includes fusion proteins capable of trapping VEGF. In a preferred embodiment, the VEGF antagonist is the fusion protein of SEQ ID NO:2 or 4; more preferably, SEQ ID NO:4. In specific embodiments, the VEGF antagonist is expressed in a mammalian cell line such as a CHO cell and may be modified post-translationally. In a specific embodiment, the fusion protein comprises amino acids 27-457 of SEQ ID NO:4 and is glycosylated at Asn residues 62, 94, 149, 222 and 308. Preferably, the VEGF antagonist is a dimer composed of two fusion proteins of SEQ ID NO:4.

[0047] The VEGF antagonist of the methods and formulations of the invention can be prepared by any suitable method known in the art, or that comes to be known. The VEGF antagonist is preferably substantially free of protein contaminants at the time it is used to prepare the pharmaceutically acceptable formulation. By “substantially free of protein contaminants” is meant, preferably, that at least 90 % of the weight of protein of the VEGF-specific fusion protein antagonist preparation used for making a formulation is VEGF fusion protein antagonist protein, more preferably at least 95%, most preferably at least 99%. The fusion protein is preferably substantially free of aggregates. “Substantially free of aggregates” means that at least 90% of the weight of fusion protein is not present in an aggregate at the time the fusion protein is used to prepare the pharmaceutically effective formulation. Unless stated otherwise, the phosphates employed are sodium phosphates and a desired buffering pH is achieved by mixing appropriate amounts of mono- and dibasic sodium phosphate.

Stable Liquid Ophthalmic Formulations

[0048] In one aspect, the invention provides a stable pharmaceutically acceptable formulation comprising a VEGF antagonist, wherein the formulation is a liquid formulation suitable for ophthalmic use. Preferably, the liquid formulation comprises a pharmaceutically effective amount of the VEGF antagonist. The formulation can also comprise one or more pharmaceutically acceptable carriers, buffers, tonicity agents, stabilizers, and/or excipients. An example of a pharmaceutically acceptable liquid formulation comprises a VEGF antagonist in a pharmaceutically effective amount, a buffer, an organic co-solvent such as polysorbate, a tonicity agent such as NaCl, and optionally, a

stabilizer such as sucrose or trehalose.

[0049] Stability is determined in a number of ways at specified time points, including determination of pH, visual inspection of color and appearance, determination of total protein content by methods known in the art, e.g., UV spectroscopy, and purity is determined by, for example, SDS-PAGE, size-exclusion HPLC, bioassay determination of activity, isoelectric focusing, and isoaspartate quantification. In one example of a bioassay useful for determining VEGF antagonist activity, a BAF/3 VEGFR1/EPOR cell line is used to determine VEGF165 binding by the VEGF antagonist of the invention.

[0050] Liquid formulations can be stored in an oxygen-deprived environment. Oxygen-deprived environments can be generated by storing the formulations under an inert gas such as, for example, nitrogen or argon. Liquid formulations are preferably stored at about 5°C.

Ophthalmic Lyophilized Formulations

[0051] In one aspect of the invention, an ophthalmically acceptable formulation comprising a VEGF antagonist is provided, wherein the formulation is a lyophilizable formulation. Lyophilizable formulations can be reconstituted into solutions, suspensions, emulsions, or any other suitable form for administration or use. Lyophilizable formulations are typically first prepared as liquids, then frozen and lyophilized. The total liquid volume before lyophilization can be less, equal to, or more than, the final reconstituted volume of the lyophilized formulation. The lyophilization process is well known to those of ordinary skill in the art, and typically includes sublimation of water from a frozen formulation under controlled conditions.

[0052] Lyophilized formulations can be stored at a wide range of temperatures. Lyophilized formulations may be stored below 25°C, for example, refrigerated at 2-8°C, or at room temperature (e.g., approximately 25°C). Preferably, lyophilized formulations are stored below about 25°C, more preferably, at about 4-20°C; below about 4°C; below about -20°C; about -40°C; about -70°C, or about -80°C. Stability of the lyophilized formulation may be determined in a number of ways known to the art, for example, by visual appearance of the cake and/or by moisture content.

[0053] Lyophilized formulations are typically reconstituted for use by addition of an aqueous solution to dissolve the lyophilized formulation. A wide variety of aqueous solutions can be used to reconstitute a lyophilized formulation. Preferably, lyophilized formulations are reconstituted using water. Lyophilized formulations are preferably reconstituted with a solution consisting essentially of

water (e.g., USP WFI, or water for injection) or bacteriostatic water (e.g., USP WFI with 0.9% benzyl alcohol). However, solutions comprising buffers and/or excipients and/or one or more pharmaceutically acceptable carries can also be used.

[0054] Freeze-dried or lyophilized formulations are typically prepared from liquids, that is, from solutions, suspensions, emulsions, and the like. Thus, the liquid that is to undergo freeze-drying or lyophilization preferably comprises all components desired in a final reconstituted liquid formulation. As a result, when reconstituted, the freeze-dried or lyophilized formulation will render a desired liquid formulation upon reconstitution.

EXAMPLES

[0055] Before the present methods are described, it is to be understood that this invention is not limited to particular methods, and experimental conditions described, as such methods and conditions may vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to be limiting, since the scope of the present invention will be limited only to the appended claims.

[0056] As used in this specification and the appended claims, the singular forms “a”, “an”, and “the” include plural references unless the context clearly dictates otherwise. Thus for example, a reference to “a method” includes one or more methods, and/or steps of the type described herein and/or which will become apparent to those persons skilled in the art upon reading this disclosure and so forth.

[0057] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, the preferred methods and materials are now described. All publications mentioned herein are incorporated herein by reference in their entirety.

Example 1. Stability of 50 mg/ml VEGF Trap Liquid Formulation Stored at 5°C in 3 ml Glass Vials.

[0058] An ophthalmic liquid formulation containing 50 mg/ml VEGF Trap (SEQ ID NO:4), 10 mM phosphate, 50 mM NaCl, 0.1% polysorbate 20, 5% sucrose, and pH 6.25, was stored at 5 °C in 3 ml glass vials and samples tested at 3, 6, 9, 12, 18 and 24 months. Stability was determined by SE-

HPLC. The results are shown in Table 1. Turbidity was measured at OD₄₀₅ nm; and percent recovered protein and purity by size exclusion HPLC.

Table 1. Stability of 50 mg/ml VEGF Trap Protein (VGFT-SS065)

Months	Visual Appearance	Turbidity (OD ₄₀₅ nm)	pH	% VEGF Trap Recovered	% VEGF Trap Native Configuration
0	Pass	0.00	6.2	100	98.8
3	Pass	0.00	6.2	101	98.7
6	Pass	0.01	6.3	100	98.3
9	Pass	0.01	6.3	101	98.3
12	Pass	0.01	6.3	104	98.4
18	Pass	0.01	6.3	96	98.1
24	Pass	0.01	6.3	105	98.1

Example 2. Stability of 50 mg/ml VEGF Trap Liquid Formulation Stored at 5°C in 3 ml Glass Vials.

[0059] A liquid formulation containing 50 mg/ml VEGF Trap (SEQ ID NO:4), 10 mM phosphate, 50 mM NaCl, 3% polyethylene glycol 3350, 5% sucrose, and pH 6.25, was stored at 5 °C in 3 ml glass vials and samples tested at 3, 6, 9, 12, 18 and 24 months. Stability results are shown in Table 2. Turbidity, percent recovered protein and purity was determined as described above.

Table 2. Stability of 50 mg/ml VEGF Trap Protein (VGFT-SS065)

Months	Visual Appearance	Turbidity	pH	% VEGF Trap Recovered	% VEGF Trap Native Configuration
0	Pass	0.00	6.2	100	98.9
3	Pass	0.00	6.1	104	98.5
6	Pass	0.01	6.3	99	98.3
9	Pass	0.00	6.3	102	97.6
12	Pass	0.01	6.3	103	98.0
18	Pass	0.00	6.3	113	97.7
24	Pass	0.00	6.2	106	97.6

Example 3. Stability of 40 mg/ml VEGF Trap Liquid Formulation Stored at 5°C in 3 ml Glass Vials.

[0060] A liquid formulation containing 40 mg/ml VEGF Trap (SEQ ID NO:4), 10 mM phosphate, 40 mM NaCl, 0.03% polysorbate 20, 5% sucrose, and pH 6.3, was stored at 5 °C in 3 ml glass vials

and samples tested at 0.5, 1, 2, 3, and 4 months. Stability results are shown in Table 3. Turbidity, percent recovered protein and purity was determined as described above.

Table 3. Stability of 40 mg/ml VEGF Trap Protein (VGFT-SS207)

Months	Visual Appearance	Turbidity	pH	% VEGF Trap Recovered	% VEGF Trap Native Configuration
0	Pass	0.00	6.3	100	99.5
0.5	Pass	0.00	6.3	99	99.4
1	Pass	0.00	6.2	98	99.5
2	Pass	0.00	6.2	95	99.2
3	Pass	0.01	6.4		
4	Pass	0.01	6.3		

Example 4. Stability of 40 mg/ml VEGF Trap Liquid Formulation Stored at 5°C in Pre-filled Glass Syringe.

[0061] A liquid formulation containing 40 mg/ml VEGF trap (SEQ ID NO:4), 10 mM phosphate, 40 mM NaCl, 0.03% polysorbate 20, 5% sucrose, and pH 6.3, was stored at 5 °C in 1 ml prefilled luer glass syringe with 4023/50 FluroTec coated plunger and samples tested at 0.5, 1, 2, 3, and 4 months. Stability results are shown in Table 4. Turbidity, percent recovered protein and purity was determined as described above.

Table 4. Stability of 40 mg/ml VEGF Trap Protein (VGFT-SS207)

Months	Visual Appearance	Turbidity	pH	% VEGF Trap Recovered	% VEGF Trap Native Configuration
0	Pass	0.00	6.3	100	99.4
0.5	Pass	0.00	6.3	100	99.3
1	Pass	0.00	6.3	100	99.4
2	Pass	0.00	6.3	97	99.1
3	Pass	0.01	6.4		
4	Pass	0.01	6.3		

Example 5. Stability of 40 mg/ml VEGF Trap Liquid Formulation Stored at 5°C in 3 ml Glass Vials.

[0062] A liquid formulation containing 40 mg/ml VEGF trap (SEQ ID NO:4), 10 mM phosphate, 135 mM NaCl, 0.03% polysorbate 20, and pH 6.3, was stored at 5 °C in 3 ml glass vials and samples

tested at 0.5, 1, 2, 3, and 4 months. Stability results are shown in Table 5. Turbidity, percent recovered protein and purity was determined as described above.

Table 5. Stability of 40 mg/ml VEGF Trap Protein (VGFT-SS203)

Months	Visual Appearance	Turbidity	pH	% VEGF Trap Recovered	% VEGF Trap Native Configuration
0	Pass	0.00	6.3	100	99.3
0.5	Pass	0.00	6.2	87	99.2
1	Pass	0.00	6.2	88	99.1
2	Pass	0.00	6.3	103	99.2
3	Pass	0.00	6.3	88	99.0
4	Pass	0.00	6.2	85	98.9
5	Pass	0.00	6.3	84	99.0

Example 6. Stability of 40 mg/ml VEGF Trap Liquid Formulation Stored at 5°C in 1 ml Pre-filled Glass Syringe.

[0063] A liquid formulation containing 40 mg/ml VEGF trap (SEQ ID NO:4), 10 mM phosphate, 135 mM NaCl, 0.03% polysorbate 20, and pH 6.3, was stored at 5 °C in 1 ml prefilled glass luer syringe with 4023/50 FluroTec coated plunger and samples tested at 0.5, 1, 2, 3, 4, and 5 months. Stability results are shown in Table 6. Turbidity, percent recovered protein and purity was determined as described above.

Table 6. Stability of 40 mg/ml VEGF Trap Protein (VGFT-SS203)

Months	Visual Appearance	Turbidity	pH	% VEGF Trap Recovered	% VEGF Trap Native Configuration
0	Pass	0.00	6.3	100	99.2
0.5	Pass	0.01	6.3	101	99.2
1	Pass	0.00	6.3	101	99.2
2	Pass	0.00	6.3	-	-
3	Pass	0.01	6.3	102	99.1
4	Pass	0.01	6.3	103	98.8
5	Pass	0.00	6.3	99	98.9

Example 7. Stability of Lyophilized 20 mg/ml VEGF Trap Formulation Stored at 5°C in 3 ml Glass Vials and Reconstituted to 40 mg/ml.

[0064] 0.8 ml of a liquid formulation containing 20 mg/ml VEGF trap (SEQ ID NO:4), 5 mM

phosphate, 20 mM NaCl, 0.015% polysorbate 20, 2.5% sucrose, and pH 6.3, were lyophilized in 3 ml glass vials. Samples were stored at 5°C and tested at 1, and 2 months. VEGF trap was reconstituted to a final concentration of 40 mg/ml VEGF Trap (final volume of 0.4 ml). Stability results are shown in Table 7 (t = time in months; * = visual appearance; **=reconstitution time). Turbidity, percent recovered protein and purity was determined as described above.

Table 7. Stability of Lyophilized 20 mg/ml VEGF Trap Protein (VGFT-SS216)

t	Vis. App.*	Recon. Time** (min)	Vis. App.* Reconst'd Liquid	Turbidity	pH	% VEGF Trap Recovered	% VEGF Trap Native Config.
0	Pass	0.6	Pass	0.00	6.3	100	99.5
1	Pass	0.6	Pass	0.01	6.3	106	99.4
2	Pass	0.4	Pass	0.01	6.2	103	99.3

Example 8. Stability of Lyophilized 20 mg/ml VEGF Trap Formulation Stored at 5°C in 3 ml Glass Vials.

[0065] 0.8 ml of a liquid formulation containing 20 mg/ml VEGF trap (SEQ ID NO:4), 5 mM phosphate, 67.5 mM NaCl, 0.015% polysorbate 20, and pH 6.3, were lyophilized in 3 ml glass vials. Samples were stored at 5°C and tested at 1, 2, and 3 months. VEGF trap was reconstituted to a final concentration of 40 mg/ml VEGF trap (final volume of 0.4 ml). Stability results are shown in Table 8 (t = time in months; * = visual appearance; **=reconstitution time).

Table 8. Stability of Lyophilized 20 mg/ml VEGF Trap Protein (VGFT-SS216)

t	Vis. App.*	Recon. Time** (min)	Vis. App. Reconst'd Liquid	Turbidity	pH	% VEGF Trap Recovered	% VEGF Trap Native Config.
0	Pass	0.7	Pass	0.00	6.3	100	99.0
1	Pass	0.7	Pass	0.01	6.2	105	98.9
2	Pass	0.4	Pass	0.01	6.2	103	98.9

WE CLAIM:

1. A prefilled glass syringe suitable for intravitreal administration containing a stable ophthalmic formulation comprising a vascular endothelial growth factor (VEGF) antagonist, an organic co-solvent, a buffer, and a stabilizing agent, wherein the VEGF antagonist is a protein produced in a Chinese Hamster Ovary (CHO) cell.
2. The prefilled glass syringe of claim 1, wherein 90% or more of the weight of the protein is not present as an aggregate.
3. The prefilled glass syringe of claim 2, wherein the protein is a fusion protein comprising the immunoglobulin-like (Ig) domain 2 of a first VEGF receptor and Ig domain 3 of a second VEGF receptor, and a multimerizing component.
4. The prefilled glass syringe of claim 3, wherein the first VEGF receptor is the human Flt1 and the second VEGF receptor is the human Flk1 or the human Flt4.
5. The prefilled glass syringe of claim 4, wherein the fusion protein comprises an amino acid sequence of SEQ ID NO:4.
6. The prefilled glass syringe of claim 5, wherein the VEGF antagonist is a dimer of the fusion protein.
7. The prefilled syringe of claim 1, wherein the organic co-solvent is selected from the group consisting of polysorbate 20, polysorbate 80, polyethylene glycol (PEG), PEG3350, and propylene glycol.
8. The prefilled syringe of claim 1, wherein the stabilizing agent is selected from the group consisting of sucrose, sorbitol, glycerol, trehalose, and mannitol.
9. The prefilled syringe of claim 1, wherein the buffer comprises phosphate.
10. The prefilled syringe of claim 4 comprising (a) 1-100 mg/ml of the VEGF antagonist; (b) 0.01-5% of the organic co-solvent; (c) 5-40 mM of the buffer; and (d) 1.0-10% of the stabilizing agent.
11. The prefilled syringe of claim 11, wherein the organic co-solvent is polysorbate 20, the buffer is phosphate, and the stabilizing agent is sucrose.

ABSTRACT

[0066] Ophthalmic formulations of a vascular endothelial growth factor (VEGF)-specific fusion protein antagonist are provided suitable for intravitreal administration to the eye. The ophthalmic formulations include a stable liquid formulation and a lyophilizable formulation. Preferably, the protein antagonist has an amino acid sequence of SEQ ID NO:4.

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**DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN
APPLICATION DATA SHEET (37 CFR 1.76)**

Title of
Invention

VEGF ANTAGONIST FORMULATIONS FOR INTRAVITREAL ADMINISTRATION

As the below named inventor, I hereby declare that:

This declaration
is directed to:

☐

The attached application, or

☒

United States application or PCT international application number 13/914,996

filed on June 11, 2013

The above-identified application was made or authorized to be made by me.

I believe that I am the original inventor or an original joint inventor of a claimed invention in the application.

I hereby acknowledge that any willful false statement made in this declaration is punishable under 18 U.S.C. 1001
by fine or imprisonment of not more than five (5) years, or both.

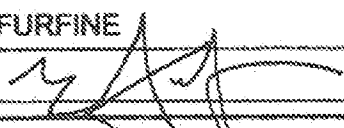
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LEGAL NAME OF INVENTOR

Inventor: Eric FURFINE

Date (Optional): 30 Jan 2014

Signature: 

Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form or must have been previously filed. Use an additional PTO/AIA/D1 form for each additional inventor.

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DECLARATION (37 CFR 1.63) FOR UTILITY OR DESIGN APPLICATION USING AN APPLICATION DATA SHEET (37 CFR 1.76)Title of
Invention**VEGF ANTAGONIST FORMULATIONS FOR INTRAVITREAL ADMINISTRATION**

As the below named inventor, I hereby declare that:

This declaration
is directed to:

The attached application, or

United States application or PCT international application number 13/914,996filed on June 11, 2013

The above-identified application was made or authorized to be made by me.

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LEGAL NAME OF INVENTORInventor: Daniel DIXDate (Optional): Jan 22, 2014Signature: *Daniel B. Dix*

Note: An application data sheet (PTO/SB/14 or equivalent), including naming the entire inventive entity, must accompany this form or must have been previously filed. Use an additional PTO/AIA/01 form for each additional inventor.

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LEGAL NAME OF INVENTOR

Inventor: Kenneth GRAHAM

Date (Optional): 19 Feb 2014

Signature: Kenneth S. Graham

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The attached application, or

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LEGAL NAME OF INVENTORInventor: Kelly FRYE

Date (Optional):

12-16-13Signature: Kelly Frye

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Electronically Filed October 12, 2018

NOTIFICATION OF PRIOR SEQUENCE LISTING Address to: Mail Stop Patent Application Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450	Attorney Docket	REGN-024CON8
	First Named Inventor	FURFINE, ERIC
	Application Number	To Be Assigned
	Filing Date	October 12, 2018
	Confirmation Number	To Be Assigned
	Group Art Unit	
	Examiner Name	
	Title:	"VEGF ANTAGONIST FORMULATIONS SUITABLE FOR INTRAVITREAL ADMINISTRATION"

Sir:

The above-identified patent application contains sequences of nucleic acid and polypeptides. A sequence listing was prepared for parent application, **15/879,294**, filed **January 24, 2018**, in paper and computer-readable format. The sequence information in the paper or compact disk copy of the sequence listing (required by 1.821(c)) of this application is identical to the sequence information in the computer-readable format of the above-identified other application. No new matter has been added. Therefore, please transfer to this application, in accordance with 37 CFR § 1.821(e), the fully compliant computer readable copy from applicants' other application. A paper (.pdf) copy of this sequence listing is enclosed.

Applicants respectfully submit that the present patent application is now in compliance with 37 CFR §§ 1.821 - 1.825. The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number REGN-024CON8.

Respectfully submitted,

BOZICEVIC, FIELD & FRANCIS LLP

Dated: 12 October 2018

By: /Karl Bozicevic, Reg. No. 28,807/

Karl Bozicevic
Registration No. 28,807

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Facsimile: (650) 327-3231

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Gln Lys Ser Leu Ser Leu Ser Pro Gly Lys
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RAW SEQUENCE LISTING

Loaded by SCORE, no errors detected.

Application Serial Number: 16159269
Source: OPAP
Date Processed by SCORE: 10/18/2018

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UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
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Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY. DOCKET NO	TOT CLAIMS	IND CLAIMS
16/159,269	10/12/2018		1720	REGN-024CON8	18	2

CONFIRMATION NO. 5813

96387

Regeneron - Bozicevic, Field & Francis
201 REDWOOD SHORES PARKWAY
SUITE 200
REDWOOD CITY, CA 94065

FILING RECEIPT



0000000103336188

Date Mailed: 10/25/2018

Receipt is acknowledged of this non-provisional patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. **If an error is noted on this Filing Receipt, please submit a written request for a Filing Receipt Correction. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections**

Inventor(s)

Eric FURFINE, Concord, MA;
Daniel DIX, LaGrangeville, NY;
Kenneth GRAHAM, Pleasant Valley, NY;
Kelly FRYE, Mendham, NJ;

Applicant(s)

REGENERON PHARMACEUTICALS, INC., Tarrytown, NY

Assignment For Published Patent Application

REGENERON PHARMACEUTICALS, INC., Tarrytown, NY

Power of Attorney: None

Domestic Priority data as claimed by applicant

This application is a CON of 15/879,294 01/24/2018
which is a CON of 15/095,606 04/11/2016 PAT 9914763
which is a CON of 14/330,096 07/14/2014 PAT 9340594
which is a CON of 13/914,996 06/11/2013 PAT 8802107
which is a CON of 13/329,770 12/19/2011 PAT 8481046
which is a CON of 12/833,417 07/09/2010 PAT 8092803
which is a CON of 12/560,885 09/16/2009 PAT 7807164
which is a DIV of 11/818,463 06/14/2007 PAT 7608261
which claims benefit of 60/814,484 06/16/2006

Foreign Applications for which priority is claimed (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see <http://www.uspto.gov> for more information.) - None.

Foreign application information must be provided in an Application Data Sheet in order to constitute a claim to foreign priority. See 37 CFR 1.55 and 1.76.

Permission to Access Application via Priority Document Exchange: Yes

Permission to Access Search Results: Yes

Applicant may provide or rescind an authorization for access using Form PTO/SB/39 or Form PTO/SB/69 as appropriate.

If Required, Foreign Filing License Granted: 10/24/2018

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 16/159,269**

Projected Publication Date: 01/31/2019

Non-Publication Request: No

Early Publication Request: No
Title

VEGF ANTAGONIST FORMULATIONS SUITABLE FOR INTRAVITREAL ADMINISTRATION

Preliminary Class

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications: No

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Since the rights granted by a U.S. patent extend only throughout the territory of the United States and have no effect in a foreign country, an inventor who wishes patent protection in another country must apply for a patent in a specific country or in regional patent offices. Applicants may wish to consider the filing of an international application under the Patent Cooperation Treaty (PCT). An international (PCT) application generally has the same effect as a regular national patent application in each PCT-member country. The PCT process **simplifies** the filing of patent applications on the same invention in member countries, but **does not result** in a grant of "an international patent" and does not eliminate the need of applicants to file additional documents and fees in countries where patent protection is desired.

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Applicants also are advised that in the case of inventions made in the United States, the Director of the USPTO must issue a license before applicants can apply for a patent in a foreign country. The filing of a U.S. patent application serves as a request for a foreign filing license. The application's filing receipt contains further information and guidance as to the status of applicant's license for foreign filing.

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Title 35, United States Code, Section 184

Title 37, Code of Federal Regulations, 5.11 & 5.15

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PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875						Application or Docket Number 16/159,269				
APPLICATION AS FILED - PART I										
(Column 1)		(Column 2)		SMALL ENTITY		OR OTHER THAN SMALL ENTITY				
FOR	NUMBER FILED	NUMBER EXTRA	RATE(\$)	FEE(\$)		RATE(\$)	FEE(\$)			
BASIC FEE (37 CFR 1.16(a), (b), or (c))	N/A	N/A	N/A			N/A	300			
SEARCH FEE (37 CFR 1.16(k), (l), or (m))	N/A	N/A	N/A			N/A	660			
EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))	N/A	N/A	N/A			N/A	760			
TOTAL CLAIMS (37 CFR 1.16(j))	18	minus 20 = *			OR	x 100 =	0.00			
INDEPENDENT CLAIMS (37 CFR 1.16(h))	2	minus 3 = *				x 460 =	0.00			
APPLICATION SIZE FEE (37 CFR 1.16(s)) If the specification and drawings exceed 100 sheets of paper, the application size fee due is \$310 (\$155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).							0.00			
							0.00			
MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))							0.00			
			TOTAL			TOTAL	1720			
* If the difference in column 1 is less than zero, enter "0" in column 2.										
APPLICATION AS AMENDED - PART II										
(Column 1)		(Column 2)		(Column 3)		SMALL ENTITY		OR OTHER THAN SMALL ENTITY		
AMENDMENT A		CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE(\$)	ADDITIONAL FEE(\$)		RATE(\$)	ADDITIONAL FEE(\$)
	Total (37 CFR 1.16(i))	*	Minus	**	=	x	=	OR	x	=
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x	=	OR	x	=
	Application Size Fee (37 CFR 1.16(s))							OR		
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	
AMENDMENT B		CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE(\$)	ADDITIONAL FEE(\$)		RATE(\$)	ADDITIONAL FEE(\$)
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	Independent (37 CFR 1.16(h))	*	Minus	***	=	x	=	OR	x	=
	Application Size Fee (37 CFR 1.16(s))							OR		
	FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))							OR		
						TOTAL ADD'L FEE		OR	TOTAL ADD'L FEE	
* If the entry in column 1 is less than the entry in column 2, write "0" in column 3. ** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20". *** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3". The "Highest Number Previously Paid For" (Total or Independent) is the highest found in the appropriate box in column 1.										

MULTIPLE DEPENDENT CLAIM FEE CALCULATION SHEET Substitute for Form PTO-1360 (For use with Form PTO/SB/06)							Application Number 16159269		Filing Date	
							Applicant(s) Eric FURFINE			
							* May be used for additional claims or amendments			
CLAIMS	AS FILED		AFTER FIRST AMENDMENT		AFTER SECOND AMENDMENT			*	*	*
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INFORMATION DISCLOSURE STATEMENT BY APPLICANT			Application Number	16/159,269	
			Filing Date	2018-10-12	
			First Named Inventor	Eric Furfine	
			Art Unit	5813	
			Examiner Name	LOCKARD, JON MCELLEND	
Sheet	1	of	1	Attorney Docket Number	REGN-024CON8

U.S. PATENT DOCUMENTS					
Examiner Initial*	Cite No.	Patent Number	Issue Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
		Number-Kind Code (if known)			
	1	6100071	2000-08-08	Davis-Smyth et al.	
	2	6897294	2005-05-24	Davis-Smyth et al.	
	3	7052691	2006-05-30	Sleeman et al.	

U.S. PATENT APPLICATION PUBLICATIONS					
Examiner Initial*	Cite No.	Publication Number	Publication Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
		Number-Kind Code (if known)			
	1	20050281831	2005-12-22	Davis-Smyth et al.	
	2	20060217311	2006-09-28	Dix et al.	
	3	20080085276	2008-04-10	Wiegand et al.	
	4	20140012227	2014-01-09	Sigg et al.	

FOREIGN PATENT DOCUMENTS						
Examiner Initial*	Cite No.	Foreign Document Number	Publication Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T
		Country Code-Number-Kind Code (if known)				
	1	WO 97/04801	1997-02-13	Genentech, Inc.		
	2	JP 10273450	1998-10-13	Toagosei Co. Ltd.		
	3	WO 99/62536	1999-12-09	Celtrix Pharmaceuticals, Inc.		
	4	WO 2004/091658	2004-10-28	Genentech, Inc.		
	5	WO 2005/000895	2005-01-06	Regeneron Pharmaceuticals, Inc.		
	6	WO 2005011734	2005-02-10	Regeneron Pharmaceuticals, Inc.		
	7	WO 2005/020972	2005-03-10	Eyetech Pharmaceuticals, Inc.		
	8	WO 2006/047325	2006-05-04	Genentech, Inc.		
	9	WO 2006/088650	2006-08-24	Regeneron Pharmaceuticals, Inc.		
	10	WO 2006/104852	2006-10-05	Regeneron Pharmaceuticals, Inc.		

NON PATENT LITERATURE DOCUMENTS			
Examiner Initials*	Cite No.	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T
	1	FRASER, Hamis M., et al., "Single Injections of Vascular Endothelial Growth Factor Trap Block Ovulation in the Macaque and Produced Prolonged, Dose-Related Suppression of Ovarian Function," (2004) J. Clin. Endocrin. & Metabol. 90(2):1114-1122	
	2	ANONYMOUS: "Lucentis in the treatment of neovascular (wet) age-related macular degeneration (AMD)", 1 January 2007, pages 1-54	

Examiner Signature		Date Considered	
--------------------	--	-----------------	--

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

Electronic Acknowledgement Receipt

EFS ID:	34532303
Application Number:	16159269
International Application Number:	
Confirmation Number:	5813
Title of Invention:	VEGF ANTAGONIST FORMULATIONS SUITABLE FOR INTRAVITREAL ADMINISTRATION
First Named Inventor/Applicant Name:	Eric FURFINE
Customer Number:	96387
Filer:	Karl Bozicevic/Savanna Fuentes
Filer Authorized By:	Karl Bozicevic
Attorney Docket Number:	REGN-024CON8
Receipt Date:	10-DEC-2018
Filing Date:	12-OCT-2018
Time Stamp:	13:04:01
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no
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File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Transmittal Letter	REGN-024CON8_2018-12-10_DS_trans.pdf	50217 9a9e15eeb940ae32cbf85a826dd2dc3b95ee7083	no	2

Warnings:

Information:					
2	Information Disclosure Statement (IDS) Form (SB08)	REGN-024CON8_2018-12-10_ID DS.pdf	27524 51302b66c8db3ab30a210e94e91d2bc63a 8cbfb8	no	1
Warnings:					
Information:					
This is not an USPTO supplied IDS fillable form					
Total Files Size (in bytes):			77741		
This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503. <u>New Applications Under 35 U.S.C. 111</u> If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application. <u>National Stage of an International Application under 35 U.S.C. 371</u> If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course. <u>New International Application Filed with the USPTO as a Receiving Office</u> If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.					

Electronically Filed 12/10/2018

INFORMATION DISCLOSURE STATEMENT Address to: Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450	Attorney Docket No.	REGN-024CON8
	Confirmation No.	5813
	First Named Inventor	Eric Furfine
	Application Number	16/159,269
	Filing Date	October 12, 2018
	Group Art Unit	
	Examiner Name	Jon McClelland Lockard
	Title: <i>"VEGF Antagonist Formulations Suitable for Intravitreal Administration"</i>	

Sir:

Applicants submit herewith documents which may be material to the examination of this application and in respect of which there may be a duty to disclose in accordance with 37 C.F.R. § 1.56. This submission is not intended to constitute an admission that any document referred to therein is "prior art" for this invention unless specifically designated as such. A listing of the documents is shown on enclosed Form PTO/SB/08A

The Examiner is requested to make the documents listed on the enclosed PTO/SB/08A of record in this application. Applicants would appreciate the Examiner initialing and returning the initialed copy of form PTO/SB/08A, indicating the documents cited therein have been considered and made of record herein.

All of the references identified herein were disclosed in parent application serial number 15/879,294, and as such, copies thereof are not included pursuant to the provisions of 37 CFR § 1.98(d).

Statements

☒ **No statement**

☐ **PTA Statement under 37 CFR § 1.704(d)(1):** Each item of information contained in the information disclosure statement filed herewith:

(i) Was first cited in any communication from a patent office in a counterpart foreign or international application or from the Office, and this communication was not received by any individual designated in § 1.56(c) more than thirty days prior to the filing of the information disclosure statement; or

(ii) Is a communication that was issued by a patent office in a counterpart foreign or international application or by the Office, and this communication was not received by any individual designated in § 1.56(c) more than thirty days prior to the filing of the information disclosure statement.

-
- ☐ **IDS Statement under 37 CFR § 1.97(e)(1):** Each item of information contained in the information disclosure statement was first cited in any communication from a foreign patent office in a counterpart foreign application not more than three months prior to the filing of the information disclosure statement; or
- ☐ **IDS Statement under 37 CFR § 1.97(e)(2):** No item of information contained in the information disclosure statement was cited in a communication from a foreign patent office in a counterpart foreign application, and, to the knowledge of the person signing the certification after making reasonable inquiry, no item of information contained in the information disclosure statement was known to any individual designated in § 1.56(c) more than three months prior to the filing of the information disclosure statement.
-

Fees

- ☒ No fee is believed to be due.
- ☐ The appropriate fee set forth in 37 C.F.R. §1.17(p) accompanies this information disclosure statement.

The Commissioner is hereby authorized to charge any underpayment of fees up to a strict limit of \$3,000.00 beyond that authorized on the credit card, but not more than \$3,000.00 in additional fees due with any communication for the above referenced patent application, including but not limited to any necessary fees for extensions of time, or credit any overpayment of any amount to Deposit Account No. 50-0815, order number REGN-024CON8.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

Date: December 10, 2018

By: /Karl Bozicevic, Reg. No. 28,807/
Karl Bozicevic, Reg. No. 28,807

BOZICEVIC, FIELD & FRANCIS LLP
201 Redwood Shores Parkway, Suite 200
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Facsimile: (650) 327-3231



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
16/159,269	10/12/2018	Eric FURFINE	REGN-024CON8

CONFIRMATION NO. 5813

96387

Regeneron - Bozicevic, Field & Francis
201 REDWOOD SHORES PARKWAY
SUITE 200
REDWOOD CITY, CA 94065

PUBLICATION NOTICE



OC000000105503510

Title: VEGF ANTAGONIST FORMULATIONS SUITABLE FOR INTRAVITREAL ADMINISTRATION

Publication No. US-2019-0031735-A1

Publication Date: 01/31/2019

NOTICE OF PUBLICATION OF APPLICATION

The above-identified application will be electronically published as a patent application publication pursuant to 37 CFR 1.211, et seq. The patent application publication number and publication date are set forth above.

The publication may be accessed through the USPTO's publically available Searchable Databases via the Internet at www.uspto.gov. The direct link to access the publication is currently <http://www.uspto.gov/patft/>.

The publication process established by the Office does not provide for mailing a copy of the publication to applicant. A copy of the publication may be obtained from the Office upon payment of the appropriate fee set forth in 37 CFR 1.19(a)(1). Orders for copies of patent application publications are handled by the USPTO's Public Records Division. The Public Records Division can be reached by telephone at (571) 272-3150 or (800) 972-6382, by facsimile at (571) 273-3250, by mail addressed to the United States Patent and Trademark Office, Public Records Division, Alexandria, VA 22313-1450 or via the Internet.

In addition, information on the status of the application, including the mailing date of Office actions and the dates of receipt of correspondence filed in the Office, may also be accessed via the Internet through the Patent Electronic Business Center at www.uspto.gov using the public side of the Patent Application Information and Retrieval (PAIR) system. The direct link to access this status information is currently <https://portal.uspto.gov/pair/PublicPair>. Prior to publication, such status information is confidential and may only be obtained by applicant using the private side of PAIR.

Further assistance in electronically accessing the publication, or about PAIR, is available by calling the Patent Electronic Business Center at 1-866-217-9197.

Office of Data Management, Application Assistance Unit (571) 272-4000, or (571) 272-4200, or 1-888-786-0101

POWER OF ATTORNEY BY APPLICANT

I hereby revoke all previous powers of attorney given in the application identified in either the attached transmittal letter or the boxes below.

Application Number	Filing Date
16/159,269	October 12, 2018

(Note: The boxes above may be left blank if information is provided on form PTO/AIA/82A.)

☒ I hereby appoint the Patent Practitioner(s) associated with the following Customer Number as my/our attorney(s) or agent(s), and to transact all business in the United States Patent and Trademark Office connected therewith for the application referenced in the attached transmittal letter (form PTO/AIA/82A) or identified above:

96387

OR

☐ I hereby appoint Practitioner(s) named in the attached list (form PTO/AIA/82C) as my/our attorney(s) or agent(s), and to transact all business in the United States Patent and Trademark Office connected therewith for the patent application referenced in the attached transmittal letter (form PTO/AIA/82A) or identified above. (Note: Complete form PTO/AIA/82C.)

Please recognize or change the correspondence address for the application identified in the attached transmittal letter or the boxes above to:

☒ The address associated with the above-mentioned Customer Number

OR

☐ The address associated with Customer Number:

OR

☐ Firm or Individual Name

Address

City

State

Zip

Country

Telephone

Email

I am the Applicant (if the Applicant is a juristic entity, list the Applicant name in the box):

Regeneron Pharmaceuticals, Inc.

- ☐ Inventor or Joint Inventor (title not required below)
- ☐ Legal Representative of a Deceased or Legally Incapacitated Inventor (title not required below)
- ☒ Assignee or Person to Whom the Inventor is Under an Obligation to Assign (provide signer's title if applicant is a juristic entity)
- ☐ Person Who Otherwise Shows Sufficient Proprietary Interest (e.g., a petition under 37 CFR 1.46(b)(2) was granted in the application or is concurrently being filed with this document) (provide signer's title if applicant is a juristic entity)

SIGNATURE of Applicant for Patent

The undersigned (whose title is supplied below) is authorized to act on behalf of the applicant (e.g., where the applicant is a juristic entity).

Signature /Frank R. Cottingham/

Date (Optional) March 13, 2019

Name Frank R. Cottingham

Title Executive Director, Assistant General Counsel, Patents, Regeneron Pharmaceuticals, Inc.

NOTE: Signature - This form must be signed by the applicant in accordance with 37 CFR 1.33. See 37 CFR 1.4 for signature requirements and certifications. If more than one applicant, use multiple forms.

☒ Total of 1 forms are submitted.

This collection of information is required by 37 CFR 1.131, 1.32, and 1.33. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 3 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Electronic Acknowledgement Receipt

EFS ID:	35422195
Application Number:	16159269
International Application Number:	
Confirmation Number:	5813
Title of Invention:	VEGF ANTAGONIST FORMULATIONS SUITABLE FOR INTRAVITREAL ADMINISTRATION
First Named Inventor/Applicant Name:	Eric FURFINE
Customer Number:	96387
Filer:	Karl Bozicevic/Savanna Fuentes
Filer Authorized By:	Karl Bozicevic
Attorney Docket Number:	REGN-024CON8
Receipt Date:	14-MAR-2019
Filing Date:	12-OCT-2018
Time Stamp:	12:59:41
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no
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File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Assignee showing of ownership per 37 CFR 3.73	REGN-024CON8_2019-03-14_373c.pdf	118252 59641a5b8e8af19477dc1195960786b44a1b5741	no	3

Warnings:

Information:					
2	Power of Attorney	REGN-024CON8_exec_POA.pdf	169061	no	1
			819f3f96148a4fcad4f06625257d880bf3fa6f ce		
Warnings:					
Information:					
Total Files Size (in bytes):				287313	
This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503. <u>New Applications Under 35 U.S.C. 111</u> If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application. <u>National Stage of an International Application under 35 U.S.C. 371</u> If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course. <u>New International Application Filed with the USPTO as a Receiving Office</u> If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.					

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

STATEMENT UNDER 37 CFR 3.73(c)Applicant/Patent Owner: Regeneron Pharmaceuticals, Inc.Application No./Patent No.: 16/159,269 Filed/Issue Date: October 12, 2018Titled: VEGF Antagonist Formulations Suitable for Intravitreal AdministrationRegeneron Pharmaceuticals, Inc., a corporation

(Name of Assignee)

(Type of Assignee, e.g., corporation, partnership, university, government agency, etc.)

states that, for the patent application/patent identified above, it is (choose **one** of options 1, 2, 3 or 4 below):

1. ☒ The assignee of the entire right, title, and interest.
2. ☐ An assignee of less than the entire right, title, and interest (check applicable box):
- ☐ The extent (by percentage) of its ownership interest is _____%. Additional Statement(s) by the owners holding the balance of the interest must be submitted to account for 100% of the ownership interest.
- ☐ There are unspecified percentages of ownership. The other parties, including inventors, who together own the entire right, title and interest are:

Additional Statement(s) by the owner(s) holding the balance of the interest must be submitted to account for the entire right, title, and interest.

3. ☐ The assignee of an undivided interest in the entirety (a complete assignment from one of the joint inventors was made). The other parties, including inventors, who together own the entire right, title, and interest are:

Additional Statement(s) by the owner(s) holding the balance of the interest must be submitted to account for the entire right, title, and interest.

4. ☐ The recipient, via a court proceeding or the like (e.g., bankruptcy, probate), of an undivided interest in the entirety (a complete transfer of ownership interest was made). The certified document(s) showing the transfer is attached.

The interest identified in option 1, 2 or 3 above (not option 4) is evidenced by either (choose **one** of options A or B below):

- A. ☒ An assignment from the inventor(s) of the patent application/patent identified above. The assignment was recorded in the United States Patent and Trademark Office at Reel 047899, Frame 0360, or for which a copy thereof is attached.
- B. ☐ A chain of title from the inventor(s), of the patent application/patent identified above, to the current assignee as follows:
1. From: _____ To: _____
- The document was recorded in the United States Patent and Trademark Office at
- Reel _____, Frame _____, or for which a copy thereof is attached.
2. From: _____ To: _____
- The document was recorded in the United States Patent and Trademark Office at
- Reel _____, Frame _____, or for which a copy thereof is attached.

[Page 1 of 2]

This collection of information is required by 37 CFR 3.73(b). The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

STATEMENT UNDER 37 CFR 3.73(c)

3. From: _____ To: _____

The document was recorded in the United States Patent and Trademark Office at
 Reel _____, Frame _____, or for which a copy thereof is attached.

4. From: _____ To: _____

The document was recorded in the United States Patent and Trademark Office at
 Reel _____, Frame _____, or for which a copy thereof is attached.

5. From: _____ To: _____

The document was recorded in the United States Patent and Trademark Office at
 Reel _____, Frame _____, or for which a copy thereof is attached.

6. From: _____ To: _____

The document was recorded in the United States Patent and Trademark Office at
 Reel _____, Frame _____, or for which a copy thereof is attached.

☐ Additional documents in the chain of title are listed on a supplemental sheet(s).

☒ As required by 37 CFR 3.73(c)(1)(i), the documentary evidence of the chain of title from the original owner to the assignee was, or concurrently is being, submitted for recordation pursuant to 37 CFR 3.11.

[NOTE: A separate copy (i.e., a true copy of the original assignment document(s)) must be submitted to Assignment Division in accordance with 37 CFR Part 3, to record the assignment in the records of the USPTO. See MPEP 302.08]

The undersigned (whose title is supplied below) is authorized to act on behalf of the assignee.

/Karl Bozicevic, Reg. No. 28,807/

2019-03-14

Signature

Date

Karl Bozicevic

28,807

Printed or Typed Name

Title or Registration Number

Privacy Act Statement

The **Privacy Act of 1974 (P.L. 93-579)** requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (*i.e.*, GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
16/159,269	10/12/2018	Eric FURFINE	REGN-024CON8

CONFIRMATION NO. 5813

POA ACCEPTANCE LETTER

96387
Regeneron - Bozicevic, Field & Francis
201 REDWOOD SHORES PARKWAY
SUITE 200
REDWOOD CITY, CA 94065



Date Mailed: 03/20/2019

NOTICE OF ACCEPTANCE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 03/14/2019.

The Power of Attorney in this application is accepted. Correspondence in this application will be mailed to the above address as provided by 37 CFR 1.33.

Questions about the contents of this notice and the requirements it sets forth should be directed to the Office of Data Management, Application Assistance Unit, at (571) 272-4000 or (571) 272-4200 or 1-888-786-0101.

/dtdinh/



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UNITED STATES DEPARTMENT OF COMMERCE
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/159,269	10/12/2018	Eric FURFINE	REGN-024CON8	5813
96387	7590	04/02/2019		
Regeneron - Bozicevic, Field & Francis 201 REDWOOD SHORES PARKWAY SUITE 200 REDWOOD CITY, CA 94065			EXAMINER LOCKARD, JON MCCLELLAND	
			ART UNIT	PAPER NUMBER
			1647	
			NOTIFICATION DATE	DELIVERY MODE
			04/02/2019	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

docket@bozpat.com

Notice of Pre-AIA or AIA Status

1. The present application is being examined under the pre-AIA first to invent provisions.

Status of Application, Amendments, and/or Claims

2. The preliminary amendment filed 12 October 2018 has been received and entered in full. Claims 1-11 have been cancelled, and claims 12-29 have been added. Therefore, claims 12-29 are pending and the subject of this Office Action.

Information Disclosure Statement

3. The information disclosure statement (IDS) submitted on 10 December 2018 has been considered by the examiner.

Specification

4. The disclosure is objected to because of the following informalities:
5. An updated status of the parent nonprovisional applications should be included in the first sentence of the specification.

Double Patenting

6. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the “right to exclude” granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim

is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

7. A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the reference application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement. A terminal disclaimer must be signed in compliance with 37 CFR 1.321(b).

8. The USPTO internet Web site contains terminal disclaimer forms which may be used. Please visit <http://www.uspto.gov/forms/>. The filing date of the application will determine what form should be used. A web-based eTerminal Disclaimer may be filled out completely online using web-screens. An eTerminal Disclaimer that meets all requirements is auto-processed and approved immediately upon submission. For more information about eTerminal Disclaimers, refer to <http://www.uspto.gov/patents/process/file/efs/guidance/eTD-info-I.jsp>.

9. Claims 12-29 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-7 and 11-17 of U.S. Patent No. 8,092,803. Although the conflicting claims are not identical, they are not patentably distinct from each other because the scope of the ophthalmic formulation of the VEGF antagonist recited in the instant claims is overlapping in scope with the ophthalmic formulation of VEGF antagonist recited in claims 1-7 and 11-17 of U.S. Patent No. 8,092,803. Therefore, the claims are overlapping in scope.

10. Claims 12-29 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-15 and 17 of U.S. Patent No. 7,608,261. Although the conflicting claims are not identical, they are not patentably distinct from each other because the

scope of the ophthalmic formulation of the VEGF antagonist recited in the instant claims is overlapping in scope with the ophthalmic formulation of VEGF antagonist recited in claims 1-15 and 17 of U.S. Patent No. 7,608,261. Therefore, the claims are overlapping in scope.

11. Claims 12-29 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-12 of U.S. Patent No. 9,340,594. Although the conflicting claims are not identical, they are not patentably distinct from each other because the scope of the ophthalmic formulation of the VEGF antagonist recited in the instant claims is overlapping in scope with the ophthalmic formulation of VEGF antagonist recited in claims 1-11 of U.S. Patent No. 9,340,594. Therefore, the claims are overlapping in scope.

12. Claims 12-29 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-12 of U.S. Patent No. 9,914,763. Although the conflicting claims are not identical, they are not patentably distinct from each other because the scope of the ophthalmic formulation of the VEGF antagonist recited in the instant claims is overlapping in scope with the ophthalmic formulation of VEGF antagonist recited in claims 1-12 of U.S. Patent No. 9,914,763. Therefore, the claims are overlapping in scope.

13. Claims 12-29 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 12-26 of copending Application 15/879,294. Although the conflicting claims are not identical, they are not patentably distinct from each other because the scope of the ophthalmic formulation of the VEGF antagonist recited in the instant

claims is overlapping in scope with the ophthalmic formulation of VEGF antagonist recited in claims 1-12 of U.S. Patent No. 9,914,763. Therefore, the claims are overlapping in scope.

This is a provisional nonstatutory double patenting rejection.

Summary

14. No claim is allowed.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon M. Lockard whose telephone number is (571) 272-2717. The examiner can normally be reached on Monday through Friday, 8:00 AM to 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joanne Hama, can be reached on (571) 272-2911. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at **866-217-9197** (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/JON M LOCKARD/
Examiner, Art Unit 1647
March 28, 2019

<i>Search Notes</i> 	Application/Control No. 16/159,269	Applicant(s)/Patent Under Reexamination FURFINE et al.
	Examiner JON M LOCKARD	Art Unit 1647

CPC - Searched*		
Symbol	Date	Examiner

CPC Combination Sets - Searched*		
Symbol	Date	Examiner

US Classification - Searched*			
Class	Subclass	Date	Examiner
	NONE	03/28/2019	JML

* See search history printout included with this form or the SEARCH NOTES box below to determine the scope of the search.

Search Notes		
Search Notes	Date	Examiner
STIC Search of SEQ ID NO:4. See search results in SCORE.	03/28/2019	JML
EAST (USPAT, US-PGPUB, EPO, DERWENT): See attached search history.	03/28/2019	JML
STN (MEDLINE, SCISEARCH, EMBASE, BIOSIS): See attached search history.	03/28/2019	JML
PALM: Inventor search.	03/28/2019	JML

Interference Search			
US Class/CPC Symbol	US Subclass/CPC Group	Date	Examiner

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EAST Search History

EAST Search History (Prior Art)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	150	vegfr1r2\$ and formulation	US-PGPUB; USPAT; EPO; DERWENT	OR	ON	2019/03/28 21:16
L2	66	l1 and (ophthalmic or intravitreal)	US-PGPUB; USPAT; EPO; DERWENT	OR	ON	2019/03/28 21:16
L3	226	(vegfr adj (trap or antagonist)) same ophthalmic	US-PGPUB; USPAT; EPO; DERWENT	OR	ON	2019/03/28 21:16
L4	54	l3 same formulation	US-PGPUB; USPAT; EPO; DERWENT	OR	ON	2019/03/28 21:16
L5	112	l2 or l4	US-PGPUB; USPAT; EPO; DERWENT	OR	ON	2019/03/28 21:17
L6	12	l5 and (ophthalmic adj formulation).clm.	US-PGPUB; USPAT; EPO; DERWENT	OR	ON	2019/03/28 21:17
L7	1061	(furfine-e\$ dix-d\$ graham-k\$ frye-k\$).in.	US-PGPUB; USPAT; EPO; DERWENT	OR	ON	2019/03/28 21:17
L8	10	l6 and l7	US-PGPUB; USPAT; EPO; DERWENT	OR	ON	2019/03/28 21:17

3/ 28/ 2019 9:18:07 PM

C:\ Users\ jlockard\ Documents\ EAST\ Workspaces\ 16159269.wsp

* * * * * STN Columbus * * * * *

=> DIS HIST

(FILE 'HOME' ENTERED AT 21:21:52 ON 28 MAR 2019)

FILE 'MEDLINE, SCISEARCH, EMBASE, BIOSIS' ENTERED AT 21:22:02 ON 28 MAR 2019

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L1          0 S VEGFR1R2? AND FORMULATION
L2          0 S VEGFR1R2 AND FORMULATION
L3          0 S (FLT1 AND (FLK1 OR FLT4)) AND FORMULATION
L4          33 S (VEGF (W) (TRAP OR ANTAGONIST)) (P) FORMULATION
L5          56 S (VEGF (W) (TRAP OR ANTAGONIST)) (P) OPHTHALMIC
L6          2 S L5 AND FORMULATION
L7          33 S L4 OR L6
L8          23 DUP REM L7 (10 DUPLICATES REMOVED)
              E FURFINE E/AU
L9          328 S E3-E7
              E DIX D/AU
L10         305 S E3 OR E8 OR E25
              E GRAHAM K/AU
L11        1036 S E3 OR E134 OR E137
              E FRYE K/AU
L12         62 S E3 OR E17
L13         10 S (L9 OR L10 OR L11 OR L12) AND VEGF AND OPHTHALMIC
L14         10 DUP REM L13 (0 DUPLICATES REMOVED)
L15         25 S L8 OR L14

```

Inventor Information for 16/159269

/J.L./

Inventor Name	City	State/Country
FURFINE, ERIC	CONCORD	MASSACHUSETTS
DIX, DANIEL	LAGRANGEVILLE	NEW YORK
GRAHAM, KENNETH	PLEASANT VALLEY	NEW YORK
FRYE, KELLY	MENDHAM	NEW JERSEY

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BIB DATA SHEET

CONFIRMATION NO. 5813

SERIAL NUMBER	FILING or 371(c) DATE	CLASS	GROUP ART UNIT	ATTORNEY DOCKET NO.	
16/159,269	10/12/2018	424	1647	REGN-024CON8	
RULE					
APPLICANTS REGENERON PHARMACEUTICALS, INC., Tarrytown, NY INVENTORS Eric FURFINE, Concord, MA; Daniel DIX, LaGrangeville, NY; Kenneth GRAHAM, Pleasant Valley, NY; Kelly FRYE, Mendham, NJ;					
** CONTINUING DATA ***** This application is a CON of 15/879,294 01/24/2018 which is a CON of 15/095,606 04/11/2016 PAT 9914763 which is a CON of 14/330,096 07/14/2014 PAT 9340594 which is a CON of 13/914,996 06/11/2013 PAT 8802107 which is a CON of 13/329,770 12/19/2011 PAT 8481046 which is a CON of 12/833,417 07/09/2010 PAT 8092803 which is a CON of 12/560,885 09/16/2009 PAT 7807164 which is a DIV of 11/818,463 06/14/2007 PAT 7608261 which claims benefit of 60/814,484 06/16/2006					
** FOREIGN APPLICATIONS *****					
** IF REQUIRED, FOREIGN FILING LICENSE GRANTED ** 10/24/2018					
Foreign Priority claimed ☐ Yes ☒ No 35 USC 119(a-d) conditions met ☐ Yes ☐ No Verified and /JON MCCLELLAND LOCKARD/ Acknowledged Examiner's Signature	☐ Met after Allowance Initials	STATE OR COUNTRY MA	SHEETS DRAWINGS 0	TOTAL CLAIMS 18	INDEPENDENT CLAIMS 2
ADDRESS Regeneron - Bozicevic, Field & Francis 201 REDWOOD SHORES PARKWAY SUITE 200 REDWOOD CITY, CA 94065 UNITED STATES					
TITLE VEGF ANTAGONIST FORMULATIONS SUITABLE FOR INTRAVITREAL ADMINISTRATION					
FILING FEE RECEIVED 1720	FEES: Authority has been given in Paper No. _____ to charge/credit DEPOSIT ACCOUNT No. _____ for following:		☐ All Fees ☐ 1.16 Fees (Filing) ☐ 1.17 Fees (Processing Ext. of time) ☐ 1.18 Fees (Issue) ☐ Other _____		

☐ Credit

INFORMATION DISCLOSURE STATEMENT BY APPLICANT			Application Number	16/159,269	
			Filing Date	2018-10-12	
			First Named Inventor	Eric Furfine	
			Art Unit	5813	
			Examiner Name	LOCKARD, JON MCELLEND	
Sheet	1	of	1	Attorney Docket Number	REGN-024CON8

U.S. PATENT DOCUMENTS					
Examiner Initial*	Cite No.	Patent Number Number-Kind Code (if known)	Issue Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	1	6100071	2000-08-08	Davis-Smyth et al.	
	2	6897294	2005-05-24	Davis-Smyth et al.	
	3	7052691	2006-05-30	Sleeman et al.	

U.S. PATENT APPLICATION PUBLICATIONS					
Examiner Initial*	Cite No.	Publication Number Number-Kind Code (if known)	Publication Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
	1	20050281831	2005-12-22	Davis-Smyth et al.	
	2	20060217311	2006-09-28	Dix et al.	
	3	20080085276	2008-04-10	Wiegand et al.	
	4	20140012227	2014-01-09	Sigg et al.	

FOREIGN PATENT DOCUMENTS						
Examiner Initial*	Cite No.	Foreign Document Number Country Code-Number-Kind Code (if known)	Publication Date YYYY-MM-DD	Name of Patentee or Applicant of Cited Document	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T
	1	WO 97/04801	1997-02-13	Genentech, Inc.		
	2	JP 10273450	1998-10-13	Toagosei Co. Ltd.		
	3	WO 99/62536	1999-12-09	Celtrix Pharmaceuticals, Inc.		
	4	WO 2004/091658	2004-10-28	Genentech, Inc.		
	5	WO 2005/000895	2005-01-06	Regeneron Pharmaceuticals, Inc.		
	6	WO 2005011734	2005-02-10	Regeneron Pharmaceuticals, Inc.		
	7	WO 2005/020972	2005-03-10	Eyetech Pharmaceuticals, Inc.		
	8	WO 2006/047325	2006-05-04	Genentech, Inc.		
	9	WO 2006/088650	2006-08-24	Regeneron Pharmaceuticals, Inc.		
	10	WO 2006/104852	2006-10-05	Regeneron Pharmaceuticals, Inc.		

NON PATENT LITERATURE DOCUMENTS				
Examiner Initials*	Cite No.	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T	
	1	FRASER, Hamis M., et al., "Single Injections of Vascular Endothelial Growth Factor Trap Block Ovulation in the Macaque and Produced Prolonged, Dose-Related Suppression of Ovarian Function," (2004) J. Clin. Endocrin. & Metabol. 90(2):1114-1122		
	2	ANONYMOUS: "Lucentis in the treatment of neovascular (wet) age-related macular degeneration (AMD)", 1 January 2007, pages 1-54		

Examiner Signature	/JON M LOCKARD/	Date Considered	03/28/2019
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*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 809. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

ALL REFERENCES CONSIDERED EXCEPT WHERE LINED THROUGH. /J.L./

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

PATENT APPLICATION FEE DETERMINATION RECORD Substitute for Form PTO-875				Application or Docket Number 16/159,269		Filing Date 10/12/2018		☐ To be Mailed				
ENTITY: ☒ LARGE ☐ SMALL ☐ MICRO												
APPLICATION AS FILED - PART I												
		(Column 1)	(Column 2)									
FOR		NUMBER FILED	NUMBER EXTRA		RATE (\$)		FEE (\$)					
☐ BASIC FEE (37 CFR 1.16(a), (b), or (c))		N/A	N/A		N/A							
☐ SEARCH FEE (37 CFR 1.16(k), (i), or (m))		N/A	N/A		N/A							
☐ EXAMINATION FEE (37 CFR 1.16(o), (p), or (q))		N/A	N/A		N/A							
TOTAL CLAIMS (37 CFR 1.16(i))		minus 20 = *		x \$100 =								
INDEPENDENT CLAIMS (37 CFR 1.16(h))		minus 3 = *		x \$460 =								
☐ APPLICATION SIZE FEE (37 CFR 1.16(s))		If the specification and drawings exceed 100 sheets of paper, the application size fee due is \$310 (\$155 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).										
☐ MULTIPLE DEPENDENT CLAIM PRESENT (37 CFR 1.16(j))												
* If the difference in column 1 is less than zero, enter "0" in column 2.					TOTAL							
APPLICATION AS AMENDED - PART II												
		(Column 1)		(Column 2)	(Column 3)							
AMENDMENT	07/22/2019	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE (\$)		ADDITIONAL FEE (\$)				
	Total (37 CFR 1.16(i))	* 18	Minus	** 20	= 0	x \$100 =		0				
	Independent (37 CFR 1.16(h))	* 2	Minus	*** 3	= 0	x \$460 =		0				
	☐ Application Size Fee (37 CFR 1.16(s))											
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))											
								TOTAL ADD'L FEE		0		
		(Column 1)		(Column 2)	(Column 3)							
AMENDMENT		CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NUMBER PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE (\$)		ADDITIONAL FEE (\$)				
	Total (37 CFR 1.16(i))	*	Minus	**	=	x \$0 =						
	Independent (37 CFR 1.16(h))	*	Minus	***	=	x \$0 =						
	☐ Application Size Fee (37 CFR 1.16(s))											
	☐ FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM (37 CFR 1.16(j))											
								TOTAL ADD'L FEE				
* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.						LIE						
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20".						/PAMELA V THERATT/						
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3".												
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.												

This collection of information is required by 37 CFR 1.16. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Electronically filed		
AMENDMENT UNDER 37 C.F.R. §1.111 Address to: Mail Stop AMENDMENT Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450	Attorney Docket No.	REGN-024CON8
	Confirmation No.	5813
	First Named Inventor	Eric Furfine
	Application Number	16/159,269
	Filing Date	October 12, 2018
	Group Art Unit	1647
	Examiner Name	Jon McClelland Lockard
	Title: <i>“VEGF Antagonist Formulations Suitable for Intravitreal Administration”</i>	

Sir:

This amendment is responsive to the Office Action dated April 2, 2019, for which a three-month period for response was given. Applicants petition for a one-month extension of time and attach the fee hereto making this amendment timely filed on or before August 2, 2019. Accordingly, this response is timely filed.

In view of the remarks put forth below, reconsideration and allowance are respectfully requested.

Amendments to the Claims are reflected in the listing of claims which begins on page 2 of this paper.

Remarks/Arguments begin on page 5 of this paper.

AMENDMENTS TO THE CLAIMS

1. – 11. (Cancelled)

12. (Currently Amended) A vial comprising:

a vascular endothelial growth factor (VEGF) antagonist,

an organic co-solvent,

a buffer, and

a stabilizing agent,

wherein the VEGF antagonist is a fusion protein produced in a Chinese Hamster Ovary (CHO) cell, the fusion protein comprising an immunoglobulin-like (Ig) domain 2 of a first VEGF receptor and Ig domain 3 of a second VEGF receptor, and a multimerizing component; **and**

wherein at least 98% of the VEGF antagonist is present in native conformation following storage at 5°C for two months as measured by size exclusion chromatography.

13. (Currently Amended) The vial of claim 12, wherein **about 99%** ~~90%~~ or more of the weight of the fusion protein is ~~not present as an aggregate~~ **in native conformation.**

14. (Previously Presented) The vial of claim 12, wherein the first VEGF receptor is human Flt1 and the second VEGF receptor is selected from the group consisting of human Flk1 and the human Flt4.

15. (Currently Amended) The vial of claim 14, wherein the fusion protein comprises **amino acids 27-457** ~~an amino acid sequence of SEQ ID NO:4.~~

16. (Currently Amended) The vial of claim ~~15~~ **14**, wherein the VEGF antagonist is a dimer of the fusion protein.

17. (Previously Presented) The vial of claim 16, wherein the organic co-solvent is selected for the group consisting of polysorbate 20, polysorbate 90, polyethylene glycol (PEG), PEG3350, and propylene glycol.

18. **(Previously Presented)** The vial of claim 17, wherein the stabilizing agent is selected from the group consisting of sucrose, sorbitol, glycerol, trehalose, and mannitol.

19. **(Currently Amended)** The vial of claim 12, wherein the organic co-solvent is polysorbate 20 and the stabilizing agent is sucrose~~buffer comprises phosphate.~~

20. **(Previously Presented)** The vial of claim 12, wherein the organic co-solvent is polysorbate 20, the buffer is phosphate, and the stabilizing agent is sucrose.

21. **(Currently Amended)** A formulation comprising:
a vascular endothelial growth factor (VEGF) antagonist,
an organic co-solvent,
a buffer, and
a stabilizing agent,
wherein the VEGF antagonist is a fusion protein produced in a Chinese Hamster Ovary (CHO) cell, the fusion protein comprising an immunoglobulin-like (Ig) domain 2 of a first VEGF receptor and Ig domain 3 of a second VEGF receptor, and a multimerizing component; **and**
wherein at least 98% of the VEGF antagonist is present in native conformation following storage at 5°C for two months as measured by size exclusion chromatography.

22. **(Currently Amended)** The formulation of claim 21, wherein about 99%~~90%~~ or more of the weight of the fusion protein is ~~not present as an aggregate~~**in native conformation.**

23. **(Previously Presented)** The formulation of claim 21, wherein the first VEGF receptor is human Flt1 and the second VEGF receptor is selected from the group consisting of human Flk1 and the human Flt4.

24. **(Currently Amended)** The formulation of claim 23, wherein the fusion protein comprises amino acids 27-457~~an amino acid sequence~~ of SEQ ID NO:4.

25. **(Currently Amended)** The formulation of claim ~~24~~²³, wherein the VEGF antagonist is a dimer of the fusion protein.

26. **(Previously Presented)** The formulation of claim 25, wherein the organic co-solvent is selected for the group consisting of polysorbate 20, polysorbate 90, polyethylene glycol (PEG), PEG3350, and propylene glycol.

27. **(Previously Presented)** The formulation of claim 26, wherein the stabilizing agent is selected from the group consisting of sucrose, sorbitol, glycerol, trehalose, and mannitol.

28. **(Currently Amended)** The formulation of claim 21, wherein the organic co-solvent is polysorbate 20 and the stabilizing agent is sucrose~~buffer comprises phosphate.~~

29. **(Previously Presented)** The formulation of claim 21, wherein the organic co-solvent is polysorbate 20, the buffer is phosphate, and the stabilizing agent is sucrose.

REMARKS

Formal Matters

Claims 12-29 are now pending in this application.

Claims 1-11 have been canceled without prejudice.

Claims 12, 13, 15, 16, 19, 21, 22, 24, 25 and 28 are amended to more particularly point out and distinctly claim the invention. The amendments are supported in the originally filed application.

No New matter has been added.

Obviousness Type Double Patenting Rejections

Claims 12-29 were rejected under the doctrine of obviousness-type double patenting over claims 1-7 and 11-17 of issued U.S. Patent 8,092,803.

Without acquiescing to the validity of the rejection and merely to expedite prosecution of the application applicants have attached hereto a Terminal Disclaimer with respect to U.S. Patent 8,092,803 thereby rendering the rejection moot.

Claims 12-29 were rejected for obviousness type-double patenting over claims 1-15 and 17 of issued U.S. Patent 7,608,261.

The rejection is respectfully traversed as applied and as it might be applied to the presently pending claims. Independent claims 12 and 21 have been amended to include an element relating to the stability of the protein conformation in storage over a period of time. This element is not contained within any of the claims of the '261 patent.

In view of distinguishing features between the claims as amended and the claims of the '261 patent the rejection should be reconsidered and withdrawn.

Claims 12-29 were rejected for obviousness-type double patenting over claims 1-12 of issued U.S. Patent 9,340,594.

The claims 1-12 of the '594 patent do not include elements relating to the percentage of the VEGF antagonist which maintains its conformation following storage over a period of time. In view of such the rejection should be reconsidered and withdrawn.

All of the pending claims also indicate that the VEGF antagonist is a fusion protein produced in a Chinese hamster ovary (CHO) cells. This feature is not contained within any of the claims of the '594 patent.

Claims 12-29 were rejected for obviousness-type double patenting over claims 1-12 of issued U.S. Patent 9,914,763. The rejection is traversed as applied and as it might be applied to the amended claims.

The claims of the '763 patent do not include elements relating to the stability of the VEGF antagonist over time when stored which element is included in the claims of the present application by amendment. In view of such the rejection should be reconsidered and withdrawn.

Claims 12-29 were rejected for obviousness-type double patenting over claims 12-26 of co-pending application 15/879,294.

The rejection is traversed as applied and as it might be applied to the presently pending claims.

None of the claims pending within the '294 application include an element relating to the stability of the VEGF antagonist over time when stored.

All of the pending claims also indicate that the VEGF antagonist is a fusion protein produced in a Chinese hamster ovary (CHO) cells. This feature is not contained within any of the claims of the '294 patent.

In view of the differences between the claims as amended and those pending within the '294 application the rejection should be reconsidered and withdrawn.

CONCLUSION

Without acquiescing to the validity of the rejection, a Terminal Disclaimer is filed with respect to U.S. Patent 8,092,803. The independent claims have been amended to include an element relating to the characterization of the formulation when stored over time, which element is included in the claims of the '803 patent, but not included within the claims of any of the other patents used in making additional obvious type double patenting rejections. In view of such, these rejections are believed to have been overcome and an indication of such is respectfully requested.

Applicants submit that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees up to a strict limit of \$3,000.00 beyond that authorized on the credit card, but not more than \$3,000.00 in additional fees due with any communication for the above referenced patent application, including but not limited to any necessary fees for extensions of time, or credit any overpayment of any amount to Deposit Account No. 50-0815, order number REGN-024CON8.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

Date: July 22, 2019

By: /Karl Bozicevic, Reg. No. 28,807/
Karl Bozicevic, Reg. No. 28,807

Attached: Terminal Disclaimer

BOZICEVIC, FIELD & FRANCIS LLP
201 Redwood Shores Parkway, Suite 200
Redwood City, CA 94065
Telephone: (650) 327-3400
Facsimile: (650) 327-3231

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

**TERMINAL DISCLAIMER TO OBIATE A DOUBLE PATENTING
REJECTION OVER A "PRIOR" PATENT**Docket Number (Optional)
REGN-024CON8

In re Application of: Eric Furfine

Application No.: 16/159,269

Filed: October 12, 2018

For: VEGF ANTAGONIST FORMULATIONS SUITABLE FOR INTRAVITREAL ADMINISTRATION

The applicant, Regeneron Pharmaceuticals, Inc., owner of 100 percent interest in the instant application hereby disclaims, except as provided below, the terminal part of the statutory term of any patent granted on the instant application which would extend beyond the expiration date of the full statutory term of **prior patent** No. 8,092,803 as the term of said **prior patent** is presently shortened by any terminal disclaimer. The applicant hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it and the **prior patent** are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon the grantee, its successors or assigns.

In making the above disclaimer, the applicant does not disclaim the terminal part of the term of any patent granted on the instant application that would extend to the expiration date of the full statutory term of the **prior patent**, "as the term of said **prior patent** is presently shortened by any terminal disclaimer," in the event that said **prior patent** later:

- expires for failure to pay a maintenance fee;
- is held unenforceable;
- is found invalid by a court of competent jurisdiction;
- is statutorily disclaimed in whole or terminally disclaimed under 37 CFR 1.321;
- has all claims canceled by a reexamination certificate;
- is reissued; or
- is in any manner terminated prior to the expiration of its full statutory term as presently shortened by any terminal disclaimer.

Check either box 1 or 2 below, if appropriate.

1. ☐ The undersigned is the applicant. If the applicant is an assignee, the undersigned is authorized to act on behalf of the assignee.

I hereby acknowledge that any willful false statements made are punishable under 18 U.S.C. 1001 by fine or imprisonment of not more than five (5) years, or both.

2. ☒ The undersigned is an attorney or agent of record. Reg. No. 28,807

/Karl Bozicevic, Reg. No. 28,807/
Signature

2019-07-22
Date

Karl Bozicevic
Typed or printed name

Partner
Title

650-833-7735
Telephone Number

- ☒ Terminal disclaimer fee under 37 CFR 1.20(d) included.

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

This collection of information is required by 37 CFR 1.321. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Privacy Act Statement

The **Privacy Act of 1974 (P.L. 93-579)** requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (*i.e.*, GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Electronic Patent Application Fee Transmittal				
Application Number:		16159269		
Filing Date:		12-Oct-2018		
Title of Invention:		VEGF ANTAGONIST FORMULATIONS SUITABLE FOR INTRAVITREAL ADMINISTRATION		
First Named Inventor/Applicant Name:		Eric FURFINE		
Filer:		Karl Bozicevic/Savanna Fuentes		
Attorney Docket Number:		REGN-024CON8		
Filed as Large Entity				
Filing Fees for Utility under 35 USC 111(a)				
Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
Extension - 1 month with \$0 paid	1251	1	200	200
Miscellaneous:				
STATUTORY OR TERMINAL DISCLAIMER	1814	1	160	160
Total in USD (\$)				360

Electronic Acknowledgement Receipt

EFS ID:	36649316
Application Number:	16159269
International Application Number:	
Confirmation Number:	5813
Title of Invention:	VEGF ANTAGONIST FORMULATIONS SUITABLE FOR INTRAVITREAL ADMINISTRATION
First Named Inventor/Applicant Name:	Eric FURFINE
Customer Number:	96387
Filer:	Karl Bozicevic/Savanna Fuentes
Filer Authorized By:	Karl Bozicevic
Attorney Docket Number:	REGN-024CON8
Receipt Date:	22-JUL-2019
Filing Date:	12-OCT-2018
Time Stamp:	14:15:28
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	CARD
Payment was successfully received in RAM	\$ 360
RAM confirmation Number	072319INTEFSW14160501
Deposit Account	
Authorized User	

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

File Listing:					
Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1		REGN-024CON8_2019-07-22_amend.pdf	47368	yes	7
			1c8221b60ed8b22277bdc47052da0aafaadcf81a		
	Multipart Description/PDF files in .zip description				
	Document Description		Start	End	
	Amendment/Req. Reconsideration-After Non-Final Reject		1	1	
	Claims		2	4	
	Applicant Arguments/Remarks Made in an Amendment		5	7	
Warnings:					
Information:					
2	Terminal Disclaimer Filed	REGN-024CON8_2019-07-22_Terminal_Disclaimer.pdf	166787	no	2
			a6e5ba3e58c06fffdac26ff357ffb13aea2be870		
Warnings:					
Information:					
3	Fee Worksheet (SB06)	fee-info.pdf	32481	no	2
			24360248181738861d773b920dd49e2fa120f252		
Warnings:					
Information:					
Total Files Size (in bytes):			246636		

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

Application Number * 16/159,269 *	Application/Control No. 16/159,269	Applicant(s)/Patent under Reexamination FURFINE et al.	
	Examiner LOCKARD, JON MCCLELLAND	Art Unit 1647	
	Document Code - DISQ		
Internal Document - DO NOT MAIL			

TERMINAL DISCLAIMER	☒ APPROVED	☐ DISAPPROVED
Date Filed: <u>22 July 2019</u>	This patent is subject to a Terminal Disclaimer	

Approved/Disapproved by:
/LAWANA R HIXON/ Technology Center: OPLC Telephone: (571)272-6074



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

NOTICE OF ALLOWANCE AND FEE(S) DUE

96387 7590 08/21/2019
Regeneron - Bozicevic, Field & Francis
201 REDWOOD SHORES PARKWAY
SUITE 200
REDWOOD CITY, CA 94065

EXAMINER	
LOCKARD, JON MCCLELLAND	
ART UNIT	PAPER NUMBER

1647

DATE MAILED: 08/21/2019

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/159,269	10/12/2018	Eric FURFINE	REGN-024CON8	5813

TITLE OF INVENTION: VEGF ANTAGONIST FORMULATIONS SUITABLE FOR INTRAVITREAL ADMINISTRATION

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	\$1000	\$0.00	\$0.00	\$1000	11/21/2019

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE DOES NOT REFLECT A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE IN THIS APPLICATION. IF AN ISSUE FEE HAS PREVIOUSLY BEEN PAID IN THIS APPLICATION (AS SHOWN ABOVE), THE RETURN OF PART B OF THIS FORM WILL BE CONSIDERED A REQUEST TO REAPPLY THE PREVIOUSLY PAID ISSUE FEE TOWARD THE ISSUE FEE NOW DUE.

HOW TO REPLY TO THIS NOTICE:

I. Review the ENTITY STATUS shown above. If the ENTITY STATUS is shown as SMALL or MICRO, verify whether entitlement to that entity status still applies.

If the ENTITY STATUS is the same as shown above, pay the TOTAL FEE(S) DUE shown above.

If the ENTITY STATUS is changed from that shown above, on PART B - FEE(S) TRANSMITTAL, complete section number 5 titled "Change in Entity Status (from status indicated above)".

For purposes of this notice, small entity fees are 1/2 the amount of undiscounted fees, and micro entity fees are 1/2 the amount of small entity fees.

II. PART B - FEE(S) TRANSMITTAL, or its equivalent, must be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed and an extra copy of the form should be submitted. If an equivalent of Part B is filed, a request to reapply a previously paid issue fee must be clearly made, and delays in processing may occur due to the difficulty in recognizing the paper as an equivalent of Part B.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Maintenance fees are due in utility patents issuing on applications filed on or after Dec. 12, 1980. It is patentee's responsibility to ensure timely payment of maintenance fees when due. More information is available at www.uspto.gov/PatentMaintenanceFees.

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), by mail or fax, or via EFS-Web.

By mail, send to: Mail Stop ISSUE FEE
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

By fax, send to: (571)-273-2885

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 5 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Use Block 1 for any change of address)

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

96387 7590 08/21/2019
Regeneron - Bozicevic, Field & Francis
201 REDWOOD SHORES PARKWAY
SUITE 200
REDWOOD CITY, CA 94065

Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being transmitted to the USPTO via EFS-Web or by facsimile to (571) 273-2885, on the date below.

(Typed or printed name)
(Signature)
(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/159,269	10/12/2018	Eric FURFINE	REGN-024CON8	5813

TITLE OF INVENTION: VEGF ANTAGONIST FORMULATIONS SUITABLE FOR INTRAVITREAL ADMINISTRATION

APPLN. TYPE	ENTITY STATUS	ISSUE FEE DUE	PUBLICATION FEE DUE	PREV. PAID ISSUE FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	UNDISCOUNTED	\$1000	\$0.00	\$0.00	\$1000	11/21/2019

EXAMINER	ART UNIT	CLASS-SUBCLASS
LOCKARD, JON MCCLELLAND	1647	424-134100

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

☐ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.

☐ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-09 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list

(1) The names of up to 3 registered patent attorneys or agents OR, alternatively,

1 _____

(2) The name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

2 _____

3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document must have been previously recorded, or filed for recordation, as set forth in 37 CFR 3.11 and 37 CFR 3.81(a). Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE

(B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent) : ☐ Individual ☐ Corporation or other private group entity ☐ Government

4a. Fees submitted: ☐ Issue Fee ☐ Publication Fee (if required) ☐ Advance Order - # of Copies _____

4b. Method of Payment: (Please first reapply any previously paid fee shown above)

☐ Electronic Payment via EFS-Web ☐ Enclosed check ☐ Non-electronic payment by credit card (Attach form PTO-2038)

☐ The Director is hereby authorized to charge the required fee(s), any deficiency, or credit any overpayment to Deposit Account No. _____

5. **Change in Entity Status** (from status indicated above)

☐ Applicant certifying micro entity status. See 37 CFR 1.29

☐ Applicant asserting small entity status. See 37 CFR 1.27

☐ Applicant changing to regular undiscounted fee status.

NOTE: Absent a valid certification of Micro Entity Status (see forms PTO/SB/15A and 15B), issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment.

NOTE: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.

NOTE: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.

NOTE: This form must be signed in accordance with 37 CFR 1.31 and 1.33. See 37 CFR 1.4 for signature requirements and certifications.

Authorized Signature _____

Date _____

Typed or printed name _____

Registration No. _____



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/159,269	10/12/2018	Eric FURFINE	REGN-024CON8	5813
96387	7590	08/21/2019	EXAMINER	
Regeneron - Bozicevic, Field & Francis 201 REDWOOD SHORES PARKWAY SUITE 200 REDWOOD CITY, CA 94065			LOCKARD, JON MCCLELLAND	
			ART UNIT	PAPER NUMBER
			1647	

DATE MAILED: 08/21/2019

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b) (Applications filed on or after May 29, 2000)

The Office has discontinued providing a Patent Term Adjustment (PTA) calculation with the Notice of Allowance.

Section 1(h)(2) of the AIA Technical Corrections Act amended 35 U.S.C. 154(b)(3)(B)(i) to eliminate the requirement that the Office provide a patent term adjustment determination with the notice of allowance. See Revisions to Patent Term Adjustment, 78 Fed. Reg. 19416, 19417 (Apr. 1, 2013). Therefore, the Office is no longer providing an initial patent term adjustment determination with the notice of allowance. The Office will continue to provide a patent term adjustment determination with the Issue Notification Letter that is mailed to applicant approximately three weeks prior to the issue date of the patent, and will include the patent term adjustment on the patent. Any request for reconsideration of the patent term adjustment determination (or reinstatement of patent term adjustment) should follow the process outlined in 37 CFR 1.705.

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at 1-(888)-786-0101 or (571)-272-4200.

OMB Clearance and PRA Burden Statement for PTOL-85 Part B

The Paperwork Reduction Act (PRA) of 1995 requires Federal agencies to obtain Office of Management and Budget approval before requesting most types of information from the public. When OMB approves an agency request to collect information from the public, OMB (i) provides a valid OMB Control Number and expiration date for the agency to display on the instrument that will be used to collect the information and (ii) requires the agency to inform the public about the OMB Control Number's legal significance in accordance with 5 CFR 1320.5(b).

The information collected by PTOL-85 Part B is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 30 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450. Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

Privacy Act Statement

The Privacy Act of 1974 (P.L. 93-579) requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (i.e., GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Notice of Allowability	Application No. 16/159,269	Applicant(s) FURFINE et al.	
	Examiner JON M LOCKARD	Art Unit 1647	AIA (FITF) Status No

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to the Amendment filed 22 July 2019.
☐ A declaration(s)/affidavit(s) under **37 CFR 1.130(b)** was/were filed on ____.

2. ☐ An election was made by the applicant in response to a restriction requirement set forth during the interview on ____; the restriction requirement and election have been incorporated into this action.

3. ☒ The allowed claim(s) is/are See Continuation Sheet. As a result of the allowed claim(s), you may be eligible to benefit from the **Patent Prosecution Highway** program at a participating intellectual property office for the corresponding application. For more information, please see http://www.uspto.gov/patents/init_events/pph/index.jsp or send an inquiry to **PPHfeedback@uspto.gov**.

4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

Certified copies:

a) ☐ All b) ☐ Some *c) ☐ None of the:

1. ☐ Certified copies of the priority documents have been received.

2. ☐ Certified copies of the priority documents have been received in Application No. ____.

3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

* Certified copies not received: ____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date ____.

Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

6. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☐ Notice of References Cited (PTO-892) 2. ☐ Information Disclosure Statements (PTO/SB/08), Paper No./Mail Date ____. 3. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material ____. 4. ☐ Interview Summary (PTO-413), Paper No./Mail Date _____.	5. ☒ Examiner's Amendment/Comment 6. ☐ Examiner's Statement of Reasons for Allowance 7. ☐ Other _____.
---	--

/J.J.L/ Examiner, Art Unit 1647	/CHRISTINE J SAUD/ Primary Examiner, Art Unit 1647
------------------------------------	---

Continuation of 3. The allowed claim(s) is/are: 12-29 (renumbered as claims 1-18, respectively)

Notice of Pre-AIA or AIA Status

1. The present application is being examined under the pre-AIA first to invent provisions.

DETAILED ACTION

Status of Application, Amendments, and/or Claims

2. The Amendment filed 22 July 2019 has been received and entered in full. Claims 12, 13, 15, 16, 19, 21, 22, 24, 25 and 28 have been amended. Therefore, claims 12-29 are pending and the subject of this Office Action.

Terminal Disclaimer

3. The terminal disclaimer filed on 22 July 2019 disclaiming the terminal portion of any patent granted on this application which would extend beyond the expiration date of **U.S. Patent No. 8,092,803** has been reviewed and is accepted. The terminal disclaimer has been recorded.

Withdrawn Objections and/or Rejections

4. The rejection of claims 12-29 on the ground of nonstatutory obviousness-type double patenting as set forth at pp. 2-5 of the previous Office action (mailed 02 April 2019) is withdrawn in view of the amended claims and the terminal disclaimer (filed 22 July 2019).

Summary

5. Claims 12-29 are allowed.

Advisory Information

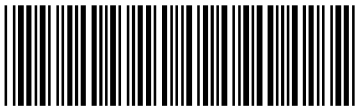
Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Jon M. Lockard** whose telephone number is **(571) 272-2717**. The examiner can normally be reached on Monday through Friday, 8:00 AM to 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Joanne Hama**, can be reached on **(571) 272-2911**. The fax number for the organization where this application or proceeding is assigned is **571-273-8300**.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at **866-217-9197** (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/J.L/
Examiner, Art Unit 1647
August 16, 2019

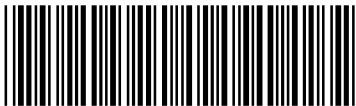
/Christine J Saoud/
Primary Examiner, Art Unit 1647

Issue Classification 	Application/Control No. 16/159,269	Applicant(s)/Patent Under Reexamination FURFINE et al.
	Examiner JON M LOCKARD	Art Unit 1647

CPC						
Symbol					Type	Version
C07K	/	14	/	71	F	2013-01-01
A61K	/	9	/	0048	I	2013-01-01
A61K	/	9	/	19	I	2013-01-01
A61K	/	38	/	1793	I	2013-01-01
C07K	/	14	/	4705	I	2013-01-01
A61M	/	5	/	178	I	2013-01-01
C07K	/	14	/	47	I	2013-01-01
A61K	/	9	/	0019	I	2013-01-01
A61K	/	38	/	179	I	2013-01-01
A61K	/	47	/	26	I	2013-01-01
A61K	/	47	/	02	I	2013-01-01
A61K	/	47	/	10	I	2013-01-01
C07K	/	2319	/	30	A	2013-01-01
C07K	/	2319	/	00	A	2013-01-01

CPC Combination Sets					
Symbol				Type	Set

/JON M LOCKARD/ Examiner, Art Unit 1647 (Assistant Examiner)	16 August 2019 (Date)	Total Claims Allowed: 18	
/CHRISTINE J SAOUD/ Primary Examiner, Art Unit 1647 (Primary Examiner)	18 August 2019 (Date)	O.G. Print Claim(s) 1	O.G. Print Figure NONE

Issue Classification 	Application/Control No. 16/159,269	Applicant(s)/Patent Under Reexamination FURFINE et al.
	Examiner JON M LOCKARD	Art Unit 1647

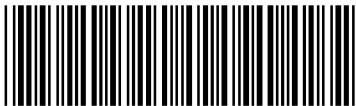
INTERNATIONAL CLASSIFICATION			
CLAIMED			
A61K	/	38	/ 18
C07K	/	14	/ 71

NON-CLAIMED			
	/		/

US ORIGINAL CLASSIFICATION	
CLASS	SUBCLASS

CROSS REFERENCES(S)						
CLASS	SUBCLASS (ONE SUBCLASS PER BLOCK)					

/JON M LOCKARD/ Examiner, Art Unit 1647 (Assistant Examiner)	16 August 2019 (Date)	Total Claims Allowed: 18	
/CHRISTINE J SAOUD/ Primary Examiner, Art Unit 1647 (Primary Examiner)	18 August 2019 (Date)	O.G. Print Claim(s) 1	O.G. Print Figure NONE

<i>Issue Classification</i> 	Application/Control No. 16/159,269	Applicant(s)/Patent Under Reexamination FURFINE et al.
	Examiner JON M LOCKARD	Art Unit 1647

☒ Claims renumbered in the same order as presented by applicant ☐ CPA ☒ T.D. ☐ R.1.47															
CLAIMS															
Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original

/JON M LOCKARD/ Examiner, Art Unit 1647 (Assistant Examiner)	16 August 2019 (Date)	Total Claims Allowed: 18	
/CHRISTINE J SAOUD/ Primary Examiner, Art Unit 1647 (Primary Examiner)	18 August 2019 (Date)	O.G. Print Claim(s) 1	O.G. Print Figure NONE

Search Notes 	Application/Control No. 16/159,269	Applicant(s)/Patent Under Reexamination FURFINE et al.
	Examiner JON M LOCKARD	Art Unit 1647

CPC - Searched*		
Symbol	Date	Examiner

CPC Combination Sets - Searched*		
Symbol	Date	Examiner

US Classification - Searched*			
Class	Subclass	Date	Examiner
	NONE	03/28/2019	JML

* See search history printout included with this form or the SEARCH NOTES box below to determine the scope of the search.

Search Notes		
Search Notes	Date	Examiner
STIC Search of SEQ ID NO:4. See search results in SCORE.	03/28/2019	JML
EAST (USPAT, US-PGPUB, EPO, DERWENT): See attached search history.	03/28/2019	JML
STN (MEDLINE, SCISEARCH, EMBASE, BIOSIS): See attached search history.	03/28/2019	JML
PALM: Inventor search.	03/28/2019	JML

Interference Search			
US Class/CPC Symbol	US Subclass/CPC Group	Date	Examiner
	STIC Search of SEQ ID NO:4. See search results in SCORE.	08/16/2019	JML
	EAST (USPAT): See attached search history.	08/16/2019	JML
	PALM: Inventor search.	08/16/2019	JML

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EAST Search History

/J.L./

EAST Search History (Interference)

Ref #	Hits	Search Query	DBs	Default Operator	Plurals	Time Stamp
L1	66	vegfr1r2\$ and formulation	USPAT	OR	ON	2019/08/16 16:26
L2	30	l1 and (ophthalmic or intravitreal)	USPAT	OR	ON	2019/08/16 16:26
L3	54	(vegf adj trap) same ophthalmic	USPAT	OR	ON	2019/08/16 16:32
L4	11	l3 same formulation	USPAT	OR	ON	2019/08/16 16:33
L5	38	l2 l4	USPAT	OR	ON	2019/08/16 16:33
L6	3	l5 and cho.clm.	USPAT	OR	ON	2019/08/16 16:35
L7	322	(furfine-e\$ dix-d\$ graham-k\$ frye-k\$).in.	USPAT	OR	ON	2019/08/16 16:36
L8	10	l5 and formulation.clm.	USPAT	OR	ON	2019/08/16 16:37
L9	8	l7 and l8	USPAT	OR	ON	2019/08/16 16:37

8/ 16/ 2019 4:37:47 PM

C:\ Users\ jlockard\ Documents\ EAST\ Workspaces\ 16159269.wsp

Inventor Information for 16/159269

/J.L./

Inventor Name	City	State/Country
FURFINE, ERIC	CONCORD	MASSACHUSETTS
DIX, DANIEL	LAGRANGEVILLE	NEW YORK
GRAHAM, KENNETH	PLEASANT VALLEY	NEW YORK
FRYE, KELLY	MENDHAM	NEW JERSEY

[App's Info](#) [Contents](#) [Patent Info](#) [Att/Agent Info](#) [Continuity Data](#) [Foreign Data](#) **Inventors** [Applicants](#) [Address](#) [Fees](#) [Post Info](#) [Pre Gr](#)

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Document Description: Issue Fee Payment (PTO-85B)

Issue Fee Transmittal Form

Application Number	Filing Date	First Named Inventor	Atty. Docket No.	Confirmation No.
16159269	12-Oct-2018	Eric FURFINE	REGN-024CON8	5813

TITLE OF INVENTION :

VEGF ANTAGONIST FORMULATIONS SUITABLE FOR INTRAVITREAL ADMINISTRATION

Entity Status	Application Type	Art Unit	Class - Subclass	EXAMINER
Regular Undiscounted	Utility under 35 USC 111(a)	1647	134100	JON LOCKARD
Issue Fee Due	Publication Due	Total Fee(s) Due	Date Due	Prev. Paid Fee
\$1000	\$0	\$1000	21-Nov-2019	\$0

1.Change of Correspondence Address and/or Indication Of Fee Address (37 CFR 1.33 & 1.363)

Current Correspondence Address:	Current Indicated Fee Address :
96387 Regeneron - Bozicevic, Field & Francis 201 REDWOOD SHORES PARKWAY SUITE 200 REDWOOD CITY CA 94065 UNITED STATES 650 327 3400 docket@bozpat.com	
☐ Change of correspondence address requested, system generated AIA/122-EFS form attached	☐ Fee Address indication requested, system generated SB/47-EFS form attached

2.Entity Status**Change in Entity Status**

Applicant certifying micro entity status; system generated Micro Entity certification form attached. See 37 CFR 1.29.

Note: Absent a valid certification of micro entity status, issue fee payment in the micro entity amount will not be accepted at the risk of application abandonment. If this box is checked, you will be prompted to choose a micro entity status on the gross income basis (37 CFR 1.29(a)) or the institution of higher education basis (37 CFR 1.29(d)), and make the applicable certification online.



Applicant asserting small entity status. See 37 CFR 1.27.

Note: If the application was previously under micro entity status, checking this box will be taken to be a notification of loss of entitlement to micro entity status.



Applicant changing to regular undiscounted fee status.

Note: Checking this box will be taken to be a notification of loss of entitlement to small or micro entity status, as applicable.



Document Description: Issue Fee Payment (PTO-85B)

3.The Following Fee(s) Are Submitted:

☒ Issue Fee

☐ I authorize USPTO to apply my previously paid issue fee to the current fees due

☐ Publication Fee

☐ The Director is hereby authorized to apply my previously paid issue fee to the current fee due and to charge deficient fees to Deposit Account Number _____

☐ Advance Order - # of copies _____

☒ If in **addition** to the payment of the issue fee amount submitted with this form, there are any discrepancies in any amount(s) due, the Director is authorized to charge any deficiency, or credit any overpayment, to Deposit Account Number 500815.
The **issue fee must be submitted** with this form. **If payment of the issue fee does not accompany this form, checking this box and providing a deposit account number will NOT be effective to satisfy full payment of the fee(s) due.**

4.Firm and/or Attorney Names To Be Printed

NOTE: If no name is listed, no name will be printed
For printing on the patent front page, list to be displayed as entered

1. KARL BOZICEVIC
2. Bozicevic, Field & Francis LLP
3.

5.Assignee Name(s) and Residence Data To Be Printed

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. If an assignee is identified below, the document has been filed for recordation as set forth in 37 CFR 3.11. Completion of this form is NOT a substitute for filing an assignment.

Name	City	State	Country	Category
REGENERON PHARMACEUTICALS, INC.	Tarrytown	NEW YORK	united states	corporation

6.Signature

I certify, in accordance with 37 CFR 1.4(d)(4) that I am an attorney or agent registered to practice before the Patent and Trademark Office who has filed and has been granted power of attorney in this application. I also certify that this Fee(s) Transmittal form is being transmitted to the USPTO via EFS-WEB on the date indicated below.

Signature	/Karl Bozicevic/	Date	09-25-2019
Name	Karl Bozicevic	Registration Number	28807

Electronic Patent Application Fee Transmittal

Application Number:	16159269			
Filing Date:	12-Oct-2018			
Title of Invention:	VEGF ANTAGONIST FORMULATIONS SUITABLE FOR INTRAVITREAL ADMINISTRATION			
First Named Inventor/Applicant Name:	Eric FURFINE			
Filer:	Karl Bozicevic/Savanna Fuentes			
Attorney Docket Number:	REGN-024CON8			
Filed as Large Entity				
Filing Fees for Utility under 35 USC 111(a)				
Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
Basic Filing:				
UTILITY APPL ISSUE FEE	1501	1	1000	1000
PUBL. FEE- EARLY, VOLUNTARY, OR NORMAL	1504	1	0	0
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				

Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
Post-Allowance-and-Post-Issuance:				
Extension-of-Time:				
Miscellaneous:				
Total in USD (\$)				1000

Electronic Acknowledgement Receipt

EFS ID:	37269012
Application Number:	16159269
International Application Number:	
Confirmation Number:	5813
Title of Invention:	VEGF ANTAGONIST FORMULATIONS SUITABLE FOR INTRAVITREAL ADMINISTRATION
First Named Inventor/Applicant Name:	Eric FURFINE
Customer Number:	96387
Filer:	Karl Bozicevic/Savanna Fuentes
Filer Authorized By:	Karl Bozicevic
Attorney Docket Number:	REGN-024CON8
Receipt Date:	25-SEP-2019
Filing Date:	12-OCT-2018
Time Stamp:	12:59:38
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	CARD
Payment was successfully received in RAM	\$ 1000
RAM confirmation Number	E20199OC59350683
Deposit Account	
Authorized User	

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

File Listing:					
Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Issue Fee Payment (PTO-85B)	Web85b.pdf	46442	no	2
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Warnings:					
Information:					
2	Fee Worksheet (SB06)	fee-info.pdf	31822	no	2
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Warnings:					
Information:					
Total Files Size (in bytes):			78264		
This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503. <u>New Applications Under 35 U.S.C. 111</u> If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application. <u>National Stage of an International Application under 35 U.S.C. 371</u> If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course. <u>New International Application Filed with the USPTO as a Receiving Office</u> If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.					



APPLICATION NO.	ISSUE DATE	PATENT NO.	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/159,269	11/05/2019	10464992	REGN-024CON8	5813

96387 7590 10/16/2019
Regeneron - Bozicevic, Field & Francis
201 REDWOOD SHORES PARKWAY
SUITE 200
REDWOOD CITY, CA 94065

ISSUE NOTIFICATION

The projected patent number and issue date are specified above.

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b) (application filed on or after May 29, 2000)

The Patent Term Adjustment is 0 day(s). Any patent to issue from the above-identified application will include an indication of the adjustment on the front page.

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) WEB site (<http://pair.uspto.gov>).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (571)-272-7702. Questions relating to issue and publication fee payments should be directed to the Application Assistance Unit (AAU) of the Office of Data Management (ODM) at (571)-272-4200.

APPLICANT(s) (Please see PAIR WEB site <http://pair.uspto.gov> for additional applicants):

REGENERON PHARMACEUTICALS, INC., Tarrytown, NY
Eric FURFINE, Concord, MA;
Daniel DIX, LaGrangeville, NY;
Kenneth GRAHAM, Pleasant Valley, NY;
Kelly FRYE, Mendham, NJ;

The United States represents the largest, most dynamic marketplace in the world and is an unparalleled location for business investment, innovation, and commercialization of new technologies. The USA offers tremendous resources and advantages for those who invest and manufacture goods here. Through SelectUSA, our nation works to encourage and facilitate business investment. To learn more about why the USA is the best country in the world to develop technology, manufacture products, and grow your business, visit SelectUSA.gov.

Electronic Acknowledgement Receipt

EFS ID:	38523697
Application Number:	16159269
International Application Number:	
Confirmation Number:	5813
Title of Invention:	VEGF ANTAGONIST FORMULATIONS SUITABLE FOR INTRAVITREAL ADMINISTRATION
First Named Inventor/Applicant Name:	Eric FURFINE
Customer Number:	96387
Filer:	Karl Bozicevic/Kimberly Zuehlke
Filer Authorized By:	Karl Bozicevic
Attorney Docket Number:	REGN-024CON8
Receipt Date:	07-FEB-2020
Filing Date:	12-OCT-2018
Time Stamp:	12:15:39
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no
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File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Request for Certificate of Correction	REGN-024CON8_2020-02-07_Cert_Correct_Petition.pdf	21956 ebeb9364bc4d5dee4be2cb62eeb9e7e7c37bfc1	no	1

Warnings:

Information:					
2	Request for Certificate of Correction	REGN-024CON8_2020-02-07_C ert_Correct.pdf	21115 a1ee1a641353a7a3f778cfb1a5b54d9610c3 46d2	no	1
Warnings:					
Information:					
Total Files Size (in bytes):			43071		
This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503. <u>New Applications Under 35 U.S.C. 111</u> If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application. <u>National Stage of an International Application under 35 U.S.C. 371</u> If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course. <u>New International Application Filed with the USPTO as a Receiving Office</u> If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.					

Electronically Filed 2/7/2020		
PETITION FOR CERTIFICATE OF CORRECTION Address to: Mail Stop Certificate of Correction Branch Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450	Attorney Docket No.	REGN-024CON8
	First Named Inventor	Eric Furfine
	Patent Number	10,464,992
	Issue Date	November 5, 2019
	Application Number	16/159,269
	Filing Date	October 12, 2018
	Title:	<i>“VEGF Antagonist Formulations Suitable for Intravitreal Administration”</i>

Sir:

Transmitted herewith for filing is a Certificate of Correction for the above-identified patent. In claim 11, line 41, please delete “90%”. This amendment was made to originally numbered claim 22 in the response filed July 22, 2019.

It is believed that no fee is due since the error was made by the Patent and Trademark Office. If for any reason a fee is found to be necessary, the Commissioner is authorized to charge such fee to Deposit Account No. 50-0815, order number REGN-024CON8.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

Date: February 7, 2020

By: /Karl Bozicevic, Reg. No. 28,807/
Karl Bozicevic
Reg. No. 28,807

BOZICEVIC, FIELD & FRANCIS LLP
201 Redwood Shores Parkway, Suite 200
Redwood City, CA 94065
Telephone: (650) 327-3400
Facsimile: (650) 327-3231

UNITED STATES PATENT AND TRADEMARK OFFICE CERTIFICATE OF CORRECTION

Page 1 of 1

PATENT NO. : 10,464,992
APPLICATION NO. : 16/159,269
ISSUE DATE : November 5, 2019
INVENTOR(S) : Eric Furfine et al.]

It is certified that an error appears or errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In claim 11, line 41, please delete "90%".

MAILING ADDRESS OF SENDER (Please do not use customer number below):

BOZICEVIC, FIELD & FRANCIS LLP
201 Redwood Shores Pkwy, Suite 200
Redwood City, California 94065

This collection of information is required by 37 CFR 1.322, 1.323, and 1.324. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1.0 hour to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Attention Certificate of Corrections Branch, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing this form, call 1-800-PTO-9199 and select option 2.

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 10,464,992 B2
APPLICATION NO. : 16/159269
DATED : November 5, 2019
INVENTOR(S) : Eric Furfine et al.

Page 1 of 1

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In the Claims

In Claim 11, Line 41, please delete "90%".

Signed and Sealed this
Third Day of March, 2020

A handwritten signature in black ink, appearing to read "Andrei Iancu", written in a cursive style.

Andrei Iancu
Director of the United States Patent and Trademark Office

**REEXAMINATION OR SUPPLEMENTAL
EXAMINATION – PATENT OWNER POWER OF
ATTORNEY OR REVOCATION OF POWER OF
ATTORNEY WITH A NEW POWER OF ATTORNEY
AND CHANGE OF CORRESPONDENCE ADDRESS
FOR REEXAMINATION OR SUPPLEMENTAL
EXAMINATION AND PATENT**

Control Number(s)	90/014,448
Filing Date(s)	2020-02-11
First Named Inventor	Eric FURFINE
Title	VEGF ANTAGONIST FORMULATIONS SUITABLE FOR INTRAVITREAL
Patent Number	10,464,992
Examiner Name	Sharon L. TURNER
Attorney Docket No(s)	1050138.00034

I. Power of Attorney. This form may be used to change the Power of Attorney in a reexamination or supplemental examination proceeding (or multiple proceedings where merged). This form may also be used to change the Power of Attorney in the patent file; in such a case, a copy of this form will be placed in both the patent file and the reexamination or supplemental examination proceeding.

A. Revocation of Previous Power of Attorney. I hereby revoke all previous patent owner powers of attorney, if any, given:

☒ in the above-identified reexamination or supplemental examination proceeding control number(s) (more than one may be changed only if the proceedings are merged).

☒ in the file of the above-identified patent.

(check BOTH boxes if change in BOTH the patent file and the reexamination or supplemental examination proceeding is requested).

B. Designation of Power of Attorney.

☐ A Power of Attorney is submitted herewith.

OR

☒ I hereby appoint Practitioner(s) associated with the Customer Number identified in the box at right as my/our attorney(s) or agent(s) to prosecute the proceeding(s)/patent identified above and selected in section I(A), and to transact all business in the United States Patent and Trademark Office connected therewith:

170744

OR

☐ I hereby appoint Practitioner(s) named below as my/our attorney(s) or agent(s) to prosecute the proceeding(s) identified above, and to transact all business in the United States Patent and Trademark Office connected therewith:

Practitioner(s) Name	Registration Number

Authorization for the Power of Attorney is provided by the signature on page 2 of this form.

This collection of information is required by 37 CFR 1.31, 1.32, and 1.33. The information is required to obtain or retain a benefit by the public, which is to update (and by the USPTO to process) the file of a patent or reexamination proceeding. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 15 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

II. Change of Correspondence Address

Please recognize or change the correspondence address for the above-identified reexamination or supplemental examination proceeding control number(s) (more than one may be changed **only** if they are merged proceedings) **and for the file of the above-identified patent** to be:

☒ The address associated with the above-identified Customer Number.

OR

☐ The address associated with the Customer Number identified in the box at right:

--

OR

☐ Firm or Individual Name				
Address				
City		State		Zip
Country				
Telephone		Email		

NOTE: THE CORRESPONDENCE ADDRESS FOR THE REEXAMINATION OR SUPPLEMENTAL EXAMINATION PROCEEDING CONTROL NUMBER(S) MUST BE THE SAME AS THAT FOR THE PATENT. SEE 37 CFR 1.33.

III. Authorization for Power of Attorney and (if selected) Change of Correspondence Address

I am the:

☐ Inventor, having ownership of the patent being reexamined.

OR

☒ Patent owner.

Statement under 37 CFR 3.73(c) (Form PTO/AIA/96) submitted herewith or filed on _____.

Signature of Inventor or Patent Owner	/ Frank R. Cottingham /	Date	08-May-2020
Name	Frank R. Cottingham, Ph.D., J.D.	Telephone	914.847.1116
Title and Company	Exec. Director & Asst. Gen. Counsel, Patents; Regeneron Pharmaceuticals, Inc.		

NOTE: Signatures of all the inventors or patent owners of the entire interest or their representative(s) are required. If more than one signature is required, submit multiple forms, check the box below, and identify the total number of forms submitted in the blank below.

☒ A total of 2 forms are submitted. If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Privacy Act Statement

The **Privacy Act of 1974 (P.L. 93-579)** requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (*i.e.*, GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Electronic Acknowledgement Receipt

EFS ID:	39494881
Application Number:	16159269
International Application Number:	
Confirmation Number:	5813
Title of Invention:	VEGF ANTAGONIST FORMULATIONS SUITABLE FOR INTRAVITREAL ADMINISTRATION
First Named Inventor/Applicant Name:	Eric FURFINE
Customer Number:	96387
Filer:	David R. Marsh/Angela Cox
Filer Authorized By:	David R. Marsh
Attorney Docket Number:	REGN-024CON8
Receipt Date:	20-MAY-2020
Filing Date:	12-OCT-2018
Time Stamp:	16:42:34
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	no
------------------------	----

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Assignee showing of ownership per 37 CFR 3.73	ReExam_373c.pdf	181767	no	3
			7748f20a8e86e8f09be5d87229e02c32b5d60b73		

Warnings:

Information:					
2	Power of Attorney	ReExam_POA.pdf	501067	no	3
			146e625f89dd50884e72bca5e0625de726d35383		
Warnings:					
Information:					
Total Files Size (in bytes):			682834		
This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503. <u>New Applications Under 35 U.S.C. 111</u> If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application. <u>National Stage of an International Application under 35 U.S.C. 371</u> If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course. <u>New International Application Filed with the USPTO as a Receiving Office</u> If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.					

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

STATEMENT UNDER 37 CFR 3.73(c)Applicant/Patent Owner: Regeneron Pharmaceuticals, Inc.Application No./Patent No.: US 90/014,448 Filed/Issue Date: 2020-02-11Titled: VEGF ANTAGONIST FORMULATIONS SUITABLE FOR INTRAVITREAL ADMINISTRATIONRegeneron Pharmaceuticals, Inc., a corporation

(Name of Assignee)

(Type of Assignee, e.g., corporation, partnership, university, government agency, etc.)

states that, for the patent application/patent identified above, it is (choose **one** of options 1, 2, 3 or 4 below):

1. ☒ The assignee of the entire right, title, and interest.
2. ☐ An assignee of less than the entire right, title, and interest (check applicable box):
- ☐ The extent (by percentage) of its ownership interest is _____. Additional Statement(s) by the owners holding the balance of the interest must be submitted to account for 100% of the ownership interest.
- ☐ There are unspecified percentages of ownership. The other parties, including inventors, who together own the entire right, title and interest are:

Additional Statement(s) by the owner(s) holding the balance of the interest must be submitted to account for the entire right, title, and interest.

3. ☐ The assignee of an undivided interest in the entirety (a complete assignment from one of the joint inventors was made). The other parties, including inventors, who together own the entire right, title, and interest are:

Additional Statement(s) by the owner(s) holding the balance of the interest must be submitted to account for the entire right, title, and interest.

4. ☐ The recipient, via a court proceeding or the like (e.g., bankruptcy, probate), of an undivided interest in the entirety (a complete transfer of ownership interest was made). The certified document(s) showing the transfer is attached.

The interest identified in option 1, 2 or 3 above (not option 4) is evidenced by either (choose **one** of options A or B below):

- A. ☒ An assignment from the inventor(s) of the patent application/patent identified above. The assignment was recorded in the United States Patent and Trademark Office at Reel 047899, Frame 0360, or for which a copy thereof is attached.
- B. ☐ A chain of title from the inventor(s), of the patent application/patent identified above, to the current assignee as follows:
1. From: _____ To: _____
- The document was recorded in the United States Patent and Trademark Office at
- Reel _____, Frame _____, or for which a copy thereof is attached.
2. From: _____ To: _____
- The document was recorded in the United States Patent and Trademark Office at
- Reel _____, Frame _____, or for which a copy thereof is attached.

[Page 1 of 2]

This collection of information is required by 37 CFR 3.73(b). The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

STATEMENT UNDER 37 CFR 3.73(c)

3. From: _____ To: _____

The document was recorded in the United States Patent and Trademark Office at
 Reel _____, Frame _____, or for which a copy thereof is attached.

4. From: _____ To: _____

The document was recorded in the United States Patent and Trademark Office at
 Reel _____, Frame _____, or for which a copy thereof is attached.

5. From: _____ To: _____

The document was recorded in the United States Patent and Trademark Office at
 Reel _____, Frame _____, or for which a copy thereof is attached.

6. From: _____ To: _____

The document was recorded in the United States Patent and Trademark Office at
 Reel _____, Frame _____, or for which a copy thereof is attached.

☐ Additional documents in the chain of title are listed on a supplemental sheet(s).

☐ As required by 37 CFR 3.73(c)(1)(i), the documentary evidence of the chain of title from the original owner to the assignee was, or concurrently is being, submitted for recordation pursuant to 37 CFR 3.11.

[NOTE: A separate copy (i.e., a true copy of the original assignment document(s)) must be submitted to Assignment Division in accordance with 37 CFR Part 3, to record the assignment in the records of the USPTO. See MPEP 302.08]

The undersigned (whose title is supplied below) is authorized to act on behalf of the assignee.

/ Frank R. Cottingham /

Signature

Frank R. Cottingham, Ph.D., J.D.

Printed or Typed Name

08-May-2020

Date

Exec. Director & Asst. Gen. Counsel, Patents

Title or Registration Number

Privacy Act Statement

The **Privacy Act of 1974 (P.L. 93-579)** requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

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1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (*i.e.*, GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
16/159,269	10/12/2018	Eric FURFINE	REGN-024CON8

CONFIRMATION NO. 5813

POA ACCEPTANCE LETTER

170744
A&P - Regeneron
601 Massachusetts Ave., NW
Washington, DC 20001



Date Mailed: 05/22/2020

NOTICE OF ACCEPTANCE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 05/20/2020.

The Power of Attorney in this application is accepted. Correspondence in this application will be mailed to the above address as provided by 37 CFR 1.33.

Questions about the contents of this notice and the requirements it sets forth should be directed to the Office of Data Management, Application Assistance Unit, at (571) 272-4000 or (571) 272-4200 or 1-888-786-0101.

/rbell/



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
16/159,269	10/12/2018	Eric FURFINE	REGN-024CON8

CONFIRMATION NO. 5813

POWER OF ATTORNEY NOTICE



OC000000117174331

96387
Regeneron - Bozicevic, Field & Francis
201 REDWOOD SHORES PARKWAY
SUITE 200
REDWOOD CITY, CA 94065

Date Mailed: 05/22/2020

NOTICE REGARDING CHANGE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 05/20/2020.

- The Power of Attorney to you in this application has been revoked by the assignee who has intervened as provided by 37 CFR 3.71. Future correspondence will be mailed to the new address of record(37 CFR 1.33).

Questions about the contents of this notice and the requirements it sets forth should be directed to the Office of Data Management, Application Assistance Unit, at (571) 272-4000 or (571) 272-4200 or 1-888-786-0101.

/rbell/

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

REGENERON PHARMACEUTICALS, INC.

Appln. No.:	16/159,269	Art Unit:	1647
Filed:	October 12, 2018	Examiner:	Jon McClelland Lockard
Patent No.:	10,464,992	Conf. No.	5813
Issued:	November 5, 2019	Atty. Docket:	1050138.00034
For:	METHOD OF MANUFACTURING VEGF ANTAGONIST FUSION PROTEINS		

**Request for Certificate of Correction of Patentee Mistakes
Under 37 C.F.R. § 1.323**

Mail Stop Certificate of Correction
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Pursuant to 37 C.F.R. § 1.323, Patentee hereby requests that a Certificate of Correction of Patentee Mistakes be issued in US Patent No. 10,464,992 (“992 Patent”), to correct patentee’s typographical error in claims 6 and 15 as follows:

6. The vial of claim 5, wherein the organic co-solvent is selected for the group consisting of polysorbate 20, polysorbate 80 [[90]], polyethylene glycol (PEG), PEG3350, and propylene glycol.

15. The formulation of claim 14, wherein the organic co-solvent is selected for the group consisting of polysorbate 20, polysorbate 80 [[90]], polyethylene glycol (PEG), PEG3350, and propylene glycol.

Patentee further submits a fee payment of \$160.00 as set forth in 37 C.F.R. § 1.20(a).

Patentee mistyped “polysorbate 80” as “polysorbate 90” in claims 6 and 15. This error originated from the Preliminary Amendment dated October 12, 2018. *See* Claims 17 and 26.

This error is “a mistake of a clerical or typographical nature,” and “of minor character.” 35 U.S.C. § 255. Both the 992 Patent and the specification as filed support this correction. The 992 Patent explicitly provides that “the organic co-solvent may be polysorbate, for example, polysorbate 20 or **polysorbate 80**, polyethylene glycol (PEG), for example, PEG 3350, or propylene glycol, or a combination thereof” Column 2, lines 25-28 (emphasis added); *see also*, column 3, lines 14-17; specification as filed, at paragraphs [0009] and [0019]. In contrast, the phrase “polysorbate 90” does not appear anywhere in the 992 Patent specification, does not exist in the art to our knowledge, and is meaningless in the context of claims 6 and 15. Further, except for the mistyped polysorbate 90, claims 6 and 15 recite the entire Markush group of five organic co-solvents in the same order as they appear in paragraphs [0009] and [0019] of the specification as filed. As such, this error is “a mistake of a clerical or typographical nature, [and] of minor character,” which qualifies for a Certificate of Correction under 35 U.S.C. § 255.

Patentee does not believe any additional fees, other than the fee specified above, are due in conjunction with this filing. However, if any additional fees are required in the present, patented application, including any fees for extensions of time, then the Commissioner is hereby authorized to charge such fees to Arnold & Porter Kaye Scholer LLP Deposit Account No. 50-2387 referencing matter number 1050138.00034.

The Commissioner is invited to contact the patentee's undersigned representative at (202) 942-6195 to address any unresolved issues remaining in this patent.

Respectfully submitted,

/Xianfeng Xu/

David R. Marsh, Ph.D. (Reg. Atty. No. 41,408)
Xianfeng Xu, Ph.D. (Reg. Atty. No. 68,376)

Date: February 26, 2021

Arnold & Porter Kaye Scholer LLP
Attn: IP Docketing
601 Massachusetts Ave, NW
Washington, D.C. 20001
(202) 942-5000 telephone
(202) 942-5999 facsimile

UNITED STATES PATENT AND TRADEMARK OFFICE CERTIFICATE OF CORRECTION

Page 1 of 1

PATENT NO. : 10,464,992
APPLICATION NO.: 16/159,269
ISSUE DATE : November 5, 2019
INVENTOR(S) : Eric FURFINE et al.

It is certified that an error appears or errors appear in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In the Claims

In Claim 6, Line 55, please change "90" to --80--.

In Claim 15, Line 54, please change "90" to --80--.

MAILING ADDRESS OF SENDER (Please do not use Customer Number below):

Arnold & Porter Kaye Scholer LLC
601 Massachusetts Ave, NW
Washington, DC 20001

This collection of information is required by 37 CFR 1.322, 1.323, and 1.324. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 1.0 hour to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Attention Certificate of Corrections Branch, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Privacy Act Statement

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The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (*i.e.*, GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.

Electronic Patent Application Fee Transmittal				
Application Number:		16159269		
Filing Date:		12-Oct-2018		
Title of Invention:		VEGF ANTAGONIST FORMULATIONS SUITABLE FOR INTRAVITREAL ADMINISTRATION		
First Named Inventor/Applicant Name:		Eric FURFINE		
Filer:		Xianfeng Xu/Angela Cox		
Attorney Docket Number:		REGN-024CON8		
Filed as Large Entity				
Filing Fees for Utility under 35 USC 111(a)				
Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
Basic Filing:				
Pages:				
Claims:				
Miscellaneous-Filing:				
Petition:				
Patent-Appeals-and-Interference:				
Post-Allowance-and-Post-Issuance:				
CERTIFICATE OF CORRECTION	1811	1	160	160

Description	Fee Code	Quantity	Amount	Sub-Total in USD(\$)
Extension-of-Time:				
Miscellaneous:				
Total in USD (\$)				160

Electronic Acknowledgement Receipt

EFS ID:	42041146
Application Number:	16159269
International Application Number:	
Confirmation Number:	5813
Title of Invention:	VEGF ANTAGONIST FORMULATIONS SUITABLE FOR INTRAVITREAL ADMINISTRATION
First Named Inventor/Applicant Name:	Eric FURFINE
Customer Number:	170744
Filer:	Xianfeng Xu
Filer Authorized By:	
Attorney Docket Number:	REGN-024CON8
Receipt Date:	26-FEB-2021
Filing Date:	12-OCT-2018
Time Stamp:	17:13:26
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment Type	CARD
Payment was successfully received in RAM	\$ 160
RAM confirmation Number	E20212PH13564035
Deposit Account	502387
Authorized User	Xianfeng Xu

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:

37 CFR 1.16 (National application filing, search, and examination fees)

37 CFR 1.17 (Patent application and reexamination processing fees)

37 CFR 1.19 (Document supply fees)
 37 CFR 1.20 (Post Issuance fees)
 37 CFR 1.21 (Miscellaneous fees and charges)

File Listing:

Document Number	Document Description	File Name	File Size(Bytes)/ Message Digest	Multi Part /.zip	Pages (if appl.)
1	Request for Certificate of Correction	Request_Regeneron.pdf	139705	no	3
			9318bc40995b09c7574bb345295a7e9d6e9073e5		

Warnings:

Information:

2	Request for Certificate of Correction	COC_Regeneron.pdf	173649	no	2
			a7216a3c1f0c7787726732445a3dfa8d5238b8e3		

Warnings:

Information:

3	Fee Worksheet (SB06)	fee-info.pdf	30306	no	2
			25ecbe21a75e31b46ecdcd8d02b8537c097e47962		

Warnings:

Information:

Total Files Size (in bytes):			343660
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This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
16/159,269	10/12/2018	Eric FURFINE	REGN-024CON8	5813
170744	7590	03/08/2021	EXAMINER	
A&P - Regeneron			LOCKARD, JON MCCLELLAND	
601 Massachusetts Ave., NW				
Washington, DC 20001				
			ART UNIT	PAPER NUMBER
			1647	
			NOTIFICATION DATE	DELIVERY MODE
			03/08/2021	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

daniel.alper@arnoldporter.com
ipdocketing@arnoldporter.com



UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450
www.uspto.gov

Patent No.: 10464992
Issue Date: 11/05/2019
Appl. No.: 16/159,269
Filed: 10/12/2018

PART (A) RESPONSE FOR CERTIFICATES OF CORRECTION

This is a decision on the Certificate of Correction request filed 26 February 2021.

The request for issuance of Certificate of Correction for the above-identified correction(s) under the provisions of 37 CFR 1.322 and/or 1.323 is hereby:

(Check one)

☒ Approved ☐ Approved in Part ☐ Denied

Comments: _____

PART (B) PETITION UNDER 37 CFR 1.324 OR 37 CFR 1.48

☐ This is a decision on the petition filed _____ to correct inventorship under 37 CFR 1.324.

☐ This is a decision on the request under 37 CFR 1.48, petition filed _____. In view of the fact that the patent has already issued, the request under 37 CFR 1.48 has been treated as a petition to correct inventorship under 37 CFR 1.324.

The petition is hereby: ☐ Granted ☐ Dismissed

Comment: _____

The patented filed is being forwarded to Certificate of Corrections Branch for issuance of a certificate naming only the actual inventor or inventors.

/JOANNE HAMA/
Supervisory Patent Examiner, Art Unit 1647
Technology Center 1600
Phone: (571)272-2911

Certificates of Correction Branch email: CustomerServiceCoC@uspto.gov CoC Central Phone Number: (703) 756-1814

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 10,464,992 B2
APPLICATION NO. : 16/159269
DATED : November 5, 2019
INVENTOR(S) : Eric Furfine et al.

Page 1 of 1

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In the Claims

In Claim 6, Line 55, please change "90" to --80--.

In Claim 15, Line 54, please change "90" to --80--.

Signed and Sealed this
Thirteenth Day of April, 2021



Drew Hirshfeld
*Performing the Functions and Duties of the
Under Secretary of Commerce for Intellectual Property and
Director of the United States Patent and Trademark Office*

AO 120 (Rev. 08/10)

TO: Mail Stop 8 Director of the U.S. Patent and Trademark Office P.O. Box 1450 Alexandria, VA 22313-1450	REPORT ON THE FILING OR DETERMINATION OF AN ACTION REGARDING A PATENT OR TRADEMARK
---	---

In Compliance with 35 U.S.C. § 290 and/or 15 U.S.C. § 1116 you are hereby advised that a court action has been
filed in the U.S. District Court Northern District of West Virginia on the following

☐ Trademarks or ☒ Patents. (☐ the patent action involves 35 U.S.C. § 292.):

DOCKET NO. 1:22-cv-61	DATE FILED 8/2/2022	U.S. DISTRICT COURT Northern District of West Virginia
PLAINTIFF REGENERON PHARMACEUTICALS, INC.		DEFENDANT MYLAN PHARMACEUTICALS, INC.
PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1 See attached		
2		
3		
4		
5		

In the above—entitled case, the following patent(s)/ trademark(s) have been included:

DATE INCLUDED	INCLUDED BY ☐ Amendment ☐ Answer ☐ Cross Bill ☐ Other Pleading	
PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
1		
2		
3		
4		
5		

In the above—entitled case, the following decision has been rendered or judgement issued:

DECISION/JUDGEMENT

CLERK CHERYL DEAN RILEY	(BY) DEPUTY CLERK /s/ D. Kinsey	DATE 8/3/2022
----------------------------	------------------------------------	------------------

Copy 1—Upon initiation of action, mail this copy to Director Copy 3—Upon termination of action, mail this copy to Director
Copy 2—Upon filing document adding patent(s), mail this copy to Director Copy 4—Case file copy

PATENT OR TRADEMARK NO.	DATE OF PATENT OR TRADEMARK	HOLDER OF PATENT OR TRADEMARK
7,070,959	July 4, 2006	Regeneron Pharmaceuticals, Inc.
9,222,106	December 29, 2015	Regeneron Pharmaceuticals, Inc.
9,254,338	February 9, 2016	Regeneron Pharmaceuticals, Inc.
9,669,069	June 6, 2017	Regeneron Pharmaceuticals, Inc.
9,816,110	November 14, 2017	Regeneron Pharmaceuticals, Inc.
10,130,681	November 20, 2018	Regeneron Pharmaceuticals, Inc.
10,406,226	September 10, 2019	Regeneron Pharmaceuticals, Inc.
10,415,055	September 17, 2019	Regeneron Pharmaceuticals, Inc.
10,464,992	November 5, 2019	Regeneron Pharmaceuticals, Inc.
10,669,594	June 2, 2020	Regeneron Pharmaceuticals, Inc.
10,857,205	December 8, 2020	Regeneron Pharmaceuticals, Inc.
10,888,601	January 12, 2021	Regeneron Pharmaceuticals, Inc.
10,927,342	February 23, 2021	Regeneron Pharmaceuticals, Inc.
10,973,879	April 13, 2021	Regeneron Pharmaceuticals, Inc.
11,053,280	July 6, 2021	Regeneron Pharmaceuticals, Inc.
11,066,458	July 20, 2021	Regeneron Pharmaceuticals, Inc.
11,084,865	August 10, 2021	Regeneron Pharmaceuticals, Inc.
11,104,715	August 31, 2021	Regeneron Pharmaceuticals, Inc.
11,174,283	November 16, 2021	Regeneron Pharmaceuticals, Inc.
11,186,625	November 30, 2021	Regeneron Pharmaceuticals, Inc.
11,253,572	February 22, 2022	Regeneron Pharmaceuticals, Inc.
11,299,532	April 12, 2022	Regeneron Pharmaceuticals, Inc.
11,306,135	April 19, 2022	Regeneron Pharmaceuticals, Inc.
11,332,771	May 17, 2022	Regeneron Pharmaceuticals, Inc.

POWER OF ATTORNEY TO PROSECUTE APPLICATIONS BEFORE THE USPTO

I hereby revoke all previous powers of attorney given in the application identified in the attached statement under 37 CFR 3.73(c).

I hereby appoint:

☒

Practitioners associated with Customer Number:

191459

OR

☐

Practitioner(s) named below (if more than ten patent practitioners are to be named, then a customer number must be used):

Name	Registration Number

Name	Registration Number

As attorney(s) or agent(s) to represent the undersigned before the United States Patent and Trademark Office (USPTO) in connection with any and all patent applications assigned only to the undersigned according to the USPTO assignment records or assignment documents attached to this form in accordance with 37 CFR 3.73(c).

Please change the correspondence address for the application identified in the attached statement under 37 CFR 3.73(c) to:

☒

The address associated with Customer Number:

191459

OR

☐

Firm or individual name

Address

City

State

Zip

Country

Telephone

Email

Assignee name and address:

Regeneron Pharmaceuticals, Inc.
777 Old Saw Mill River Road
Tarrytown, NY 10591-6707

A copy of this form, together with a statement under 37 CFR 3.73(c) (Form PTO/AIA/96 or equivalent) is required to be filed in each application in which this form is used. The statement under 37 CFR 3.73(c) may be completed by one of the practitioners appointed in this form, and must identify the application in which this Power of Attorney is to be filed.

SIGNATURE of Assignee of Record

The individual whose signature and title is supplied below is authorized to act on behalf of the assignee.

Signature /Frank R. Cottingham/

Date 13 January 2023

Name Frank R. Cottingham, Ph.D., J.D.

Telephone

Title Vice President, Associate General Counsel, Intellectual Property

This collection of information is required by 37 CFR 1.31, 1.32, and 1.33. The information is required to obtain or retain a benefit by the public, which is to update (and by the USPTO to process) the file of a patent or reexamination proceeding. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 18 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

Privacy Act Statement

The **Privacy Act of 1974 (P.L. 93-579)** requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
3. A record in this system of records may be disclosed, as a routine use, to a Member of Congress submitting a request involving an individual, to whom the record pertains, when the individual has requested assistance from the Member with respect to the subject matter of the record.
4. A record in this system of records may be disclosed, as a routine use, to a contractor of the Agency having need for the information in order to perform a contract. Recipients of information shall be required to comply with the requirements of the Privacy Act of 1974, as amended, pursuant to 5 U.S.C. 552a(m).
5. A record related to an International Application filed under the Patent Cooperation Treaty in this system of records may be disclosed, as a routine use, to the International Bureau of the World Intellectual Property Organization, pursuant to the Patent Cooperation Treaty.
6. A record in this system of records may be disclosed, as a routine use, to another federal agency for purposes of National Security review (35 U.S.C. 181) and for review pursuant to the Atomic Energy Act (42 U.S.C. 218(c)).
7. A record from this system of records may be disclosed, as a routine use, to the Administrator, General Services, or his/her designee, during an inspection of records conducted by GSA as part of that agency's responsibility to recommend improvements in records management practices and programs, under authority of 44 U.S.C. 2904 and 2906. Such disclosure shall be made in accordance with the GSA regulations governing inspection of records for this purpose, and any other relevant (*i.e.*, GSA or Commerce) directive. Such disclosure shall not be used to make determinations about individuals.
8. A record from this system of records may be disclosed, as a routine use, to the public after either publication of the application pursuant to 35 U.S.C. 122(b) or issuance of a patent pursuant to 35 U.S.C. 151. Further, a record may be disclosed, subject to the limitations of 37 CFR 1.14, as a routine use, to the public if the record was filed in an application which became abandoned or in which the proceedings were terminated and which application is referenced by either a published application, an application open to public inspection or an issued patent.
9. A record from this system of records may be disclosed, as a routine use, to a Federal, State, or local law enforcement agency, if the USPTO becomes aware of a violation or potential violation of law or regulation.



ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #
16/159,269

RECEIPT DATE / TIME
02/28/2023 04:30:17 PM ET

ATTORNEY DOCKET #
REGN-024CON8

Title of Invention

VEGF ANTAGONIST FORMULATIONS SUITABLE FOR INTRAVITREAL ADMINISTRATION

Application Information

APPLICATION TYPE Utility - Nonprovisional Application
under 35 USC 111(a)

PATENT # 10464992

CONFIRMATION # 5813

FILED BY Kathi Moore

PATENT CENTER # 61663998

FILING DATE 10/12/2018

CUSTOMER # 170744

FIRST NAMED INVENTOR Eric FURFINE

CORRESPONDENCE ADDRESS -

AUTHORIZED BY Michael Lewis

Documents

TOTAL DOCUMENTS: 2

DOCUMENT	PAGES	DESCRIPTION	SIZE (KB)
P35063US10-373c.pdf	3	Assignee showing of ownership per 37 CFR 3.73	110 KB
POA-Regeneron.pdf	2	Power of Attorney	3810 KB

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
P35063US10-373c.pdf	BDB81E9574AAF9B73016A968FB7D187935E222F02606A2B1C6 858A4598A30990901E95A8F3175C0AE16B762FDF8E9BB66A19 5FCBE877D4C7BFFCE9DB8F812531

POA-Regeneron.pdf

BDECE05D2F51BBCDB37E674E496644E6B6A6D74B020A14B4
FE816D8015E1EC9283171078BA0A0E1076CA395ADB4C661BA
9E9C16DA415BC049CBFF10B715A0675

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

STATEMENT UNDER 37 CFR 3.73(c)Applicant/Patent Owner: Regeneron Pharmaceuticals, Inc.Application No./Patent No.: 10,464,992Filed/Issue Date: November 5, 2019Titled: VEGF Antagonist Formulations Suitable for Intravitreal AdministrationRegeneron Pharmaceuticals, Inc., a corporation

(Name of Assignee)

(Type of Assignee, e.g., corporation, partnership, university, government agency, etc.)

states that, for the patent application/patent identified above, it is (choose **one** of options 1, 2, 3 or 4 below):

1. ☒ The assignee of the entire right, title, and interest.
2. ☐ An assignee of less than the entire right, title, and interest (check applicable box):
- ☐ The extent (by percentage) of its ownership interest is ____%. Additional Statement(s) by the owners holding the balance of the interest must be submitted to account for 100% of the ownership interest.
- ☐ There are unspecified percentages of ownership. The other parties, including inventors, who together own the entire right, title and interest are:

Additional Statement(s) by the owner(s) holding the balance of the interest must be submitted to account for the entire right, title, and interest.

3. ☐ The assignee of an undivided interest in the entirety (a complete assignment from one of the joint inventors was made). The other parties, including inventors, who together own the entire right, title, and interest are:

Additional Statement(s) by the owner(s) holding the balance of the interest must be submitted to account for the entire right, title, and interest.

4. ☐ The recipient, via a court proceeding or the like (e.g., bankruptcy, probate), of an undivided interest in the entirety (a complete transfer of ownership interest was made). The certified document(s) showing the transfer is attached.

The interest identified in option 1, 2 or 3 above (not option 4) is evidenced by either (choose **one** of options A or B below):

- A. ☒ An assignment from the inventor(s) of the patent application/patent identified above. The assignment was recorded in the United States Patent and Trademark Office at Reel 047899, Frame 0360, or for which a copy thereof is attached.
- B. ☐ A chain of title from the inventor(s), of the patent application/patent identified above, to the current assignee as follows:
1. From: _____ To: _____
- The document was recorded in the United States Patent and Trademark Office at
- Reel _____, Frame _____, or for which a copy thereof is attached.
2. From: _____ To: _____
- The document was recorded in the United States Patent and Trademark Office at
- Reel _____, Frame _____, or for which a copy thereof is attached.

[Page 1 of 2]

This collection of information is required by 37 CFR 3.73(b). The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. **SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.**

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.

STATEMENT UNDER 37 CFR 3.73(c)

3. From: _____ To: _____

The document was recorded in the United States Patent and Trademark Office at
 Reel _____, Frame _____, or for which a copy thereof is attached.

4. From: _____ To: _____

The document was recorded in the United States Patent and Trademark Office at
 Reel _____, Frame _____, or for which a copy thereof is attached.

5. From: _____ To: _____

The document was recorded in the United States Patent and Trademark Office at
 Reel _____, Frame _____, or for which a copy thereof is attached.

6. From: _____ To: _____

The document was recorded in the United States Patent and Trademark Office at
 Reel _____, Frame _____, or for which a copy thereof is attached.

☐ Additional documents in the chain of title are listed on a supplemental sheet(s).

☐ As required by 37 CFR 3.73(c)(1)(i), the documentary evidence of the chain of title from the original owner to the assignee was, or concurrently is being, submitted for recordation pursuant to 37 CFR 3.11.

[NOTE: A separate copy (i.e., a true copy of the original assignment document(s)) must be submitted to Assignment Division in accordance with 37 CFR Part 3, to record the assignment in the records of the USPTO. See MPEP 302.08]

The undersigned (whose title is supplied below) is authorized to act on behalf of the assignee.

/Michael W. Lewis/

Signature

Michael W. Lewis

Printed or Typed Name

February 28, 2023

Date

76,829

Title or Registration Number

Privacy Act Statement

The **Privacy Act of 1974 (P.L. 93-579)** requires that you be given certain information in connection with your submission of the attached form related to a patent application or patent. Accordingly, pursuant to the requirements of the Act, please be advised that: (1) the general authority for the collection of this information is 35 U.S.C. 2(b)(2); (2) furnishing of the information solicited is voluntary; and (3) the principal purpose for which the information is used by the U.S. Patent and Trademark Office is to process and/or examine your submission related to a patent application or patent. If you do not furnish the requested information, the U.S. Patent and Trademark Office may not be able to process and/or examine your submission, which may result in termination of proceedings or abandonment of the application or expiration of the patent.

The information provided by you in this form will be subject to the following routine uses:

1. The information on this form will be treated confidentially to the extent allowed under the Freedom of Information Act (5 U.S.C. 552) and the Privacy Act (5 U.S.C. 552a). Records from this system of records may be disclosed to the Department of Justice to determine whether disclosure of these records is required by the Freedom of Information Act.
2. A record from this system of records may be disclosed, as a routine use, in the course of presenting evidence to a court, magistrate, or administrative tribunal, including disclosures to opposing counsel in the course of settlement negotiations.
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APPLICATION NUMBER	FILING OR 371(C) DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
16/159,269	10/12/2018	Eric FURFINE	REGN-024CON8

CONFIRMATION NO. 5813

POWER OF ATTORNEY NOTICE



OC000000137528538

Date Mailed: 03/08/2023

170744
A&P - Regeneron
601 Massachusetts Ave., NW
Washington, DC 20001

NOTICE REGARDING CHANGE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 02/28/2023.

- The Power of Attorney to you in this application has been revoked by the assignee who has intervened as provided by 37 CFR 3.71. Future correspondence will be mailed to the new address of record(37 CFR 1.33).

Questions about the contents of this notice and the requirements it sets forth should be directed to the Office of Data Management, Application Assistance Unit, at (571) 272-4000 or (571) 272-4200 or 1-888-786-0101.

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APPLICATION NUMBER	FILING or 371(c) DATE	GRP ART UNIT	FIL FEE REC'D	ATTY. DOCKET NO	TOT CLAIMS	IND CLAIMS
16/159,269	10/12/2018	1647	1720	REGN-024CON8	18	2

CONFIRMATION NO. 5813

CORRECTED FILING RECEIPT

191459

A&P - Regeneron (Prosecution)
601 Massachusetts Ave., NW
Washington, DC 20001-3743



Date Mailed: 03/08/2023

Receipt is acknowledged of this non-provisional utility patent application. The application will be taken up for examination in due course. Applicant will be notified as to the results of the examination. Any correspondence concerning the application must include the following identification information: the U.S. APPLICATION NUMBER, FILING DATE, NAME OF FIRST INVENTOR, and TITLE OF INVENTION. Fees transmitted by check or draft are subject to collection.

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Inventor(s)

Eric FURFINE, Concord, MA;
Daniel DIX, LaGrangeville, NY;
Kenneth GRAHAM, Pleasant Valley, NY;
Kelly FRYE, Mendham, NJ;

Applicant(s)

REGENERON PHARMACEUTICALS, INC., Tarrytown, NY

Assignment For Published Patent Application

REGENERON PHARMACEUTICALS, INC., Tarrytown, NY

Power of Attorney: The patent practitioners associated with Customer Number 191459

Domestic Priority data as claimed by applicant

This application is a CON of 15/879,294 01/24/2018 PAT 10400025
which is a CON of 15/095,606 04/11/2016 PAT 9914763
which is a CON of 14/330,096 07/14/2014 PAT 9340594
which is a CON of 13/914,996 06/11/2013 PAT 8802107
which is a CON of 13/329,770 12/19/2011 PAT 8481046
which is a CON of 12/833,417 07/09/2010 PAT 8092803
which is a CON of 12/560,885 09/16/2009 PAT 7807164
which is a DIV of 11/818,463 06/14/2007 PAT 7608261
which claims benefit of 60/814,484 06/16/2006

Foreign Applications for which priority is claimed (You may be eligible to benefit from the **Patent Prosecution Highway** program at the USPTO. Please see <http://www.uspto.gov> for more information.) - None.

Foreign application information must be provided in an Application Data Sheet in order to constitute a claim to foreign priority. See 37 CFR 1.55 and 1.76.

Permission to Access Application via Priority Document Exchange: Yes

Permission to Access Search Results: Yes

Applicant may provide or rescind an authorization for access using Form PTO/SB/39 or Form PTO/SB/69 as appropriate.

If Required, Foreign Filing License Granted: 10/24/2018

The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is **US 16/159,269**

Projected Publication Date: Not Applicable

Non-Publication Request: No

Early Publication Request: No

Title

VEGF ANTAGONIST FORMULATIONS SUITABLE FOR INTRAVITREAL ADMINISTRATION

Preliminary Class

424

Statement under 37 CFR 1.55 or 1.78 for AIA (First Inventor to File) Transition Applications: No

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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

CELLTRION, INC.,
Petitioner,

v.

REGENERON PHARMACEUTICALS, INC.,
Patent Owner.

IPR2023-00462
Patent 10,464,992 B2

Before JOHN G. NEW, SUSAN L. C. MITCHELL, and JAMIE T. WISZ,
Administrative Patent Judges.

WISZ, *Administrative Patent Judge.*

DECISION
Granting Institution of *Inter Partes* Review
35 U.S.C. § 314

I. INTRODUCTION

Celltrion, Inc. (“Petitioner”) filed a Petition (Paper 2, “Pet.”) requesting an *inter partes* review of claims 1–18 of U.S. Patent No. 10,464,992 (Ex. 1001, “the ’992 patent”). Regeneron Pharmaceuticals, Inc. (“Patent Owner”) filed a Preliminary Response (Paper 6, “Prelim. Resp.”). With Board authorization, Petitioner filed a Pre-Institution Reply (Paper 9, “Reply”), and Patent Owner filed a Sur-Reply (Paper 10, “Sur-Reply”).

Under 35 U.S.C. § 314(a), the Board “may not authorize an *inter partes* review to be instituted unless . . . the information presented in the petition . . . and any response . . . shows that there is a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition.” After considering the Petition, the Preliminary Response, the Reply, the Sur-reply, and the evidence of record, we determine that Petitioner has demonstrated a reasonable likelihood of prevailing with respect to at least one claim challenged in the Petition. Accordingly, we institute an *inter partes* review of claims 1–18 of the ’992 patent, based on all of the grounds identified in the Petition. *See SAS Inst. Inc. v. Iancu*, 138 S. Ct. 1348, 1354, 1359–60 (2018); 37 C.F.R. § 42.108(a) (“When instituting post-grant review, the Board will authorize the review to proceed on all of the challenged claims and on all grounds of unpatentability asserted for each claim.”).

The following findings of fact and conclusions of law are not final, but are made for the sole purpose of determining whether Petitioner meets the threshold for initiating review. Any final decision shall be based on the full trial record, including any response timely filed by Patent Owner. Any arguments not raised by Patent Owner in a timely-filed Response may be deemed waived, even if they were presented in the Preliminary Response.

II. BACKGROUND

A. *Real Parties-in-Interest*

Petitioner identifies Celltrion, Inc., Celltrion Healthcare Co. Ltd. and Celltrion Healthcare U.S.A., Inc. as the real parties-in-interest. Pet. 39. Patent Owner identifies Regeneron Pharmaceuticals, Inc. as the real party-in-interest. Paper 4, 1.

B. *Related Matters*

The parties identify the following district court litigation involving the '992 patent: *Regeneron Pharmaceuticals, Inc. v. Mylan Pharmaceuticals Inc.*, Case No. 1-22-cv-00061 (N.D.W.V), filed on August 2, 2022. Pet. 39; Paper 4, 1.

The parties identify two matters related to the '992 patent filed at the USPTO: (1) *ex parte* reexamination Control No. 90/014,448 (pending); (2) *Chengdu Kanghong Biotechnology Co., Ltd. v. Regeneron Pharms., Inc.*, IPR2021-00402 (PTAB Jan. 7, 2021) (terminated). Pet. 39; Paper 4, 1.

Patent Owner identifies other *inter partes* review proceedings challenging related patents. See Paper 4, 1–3. The pending proceedings (excluding joined cases) include:

Mylan Pharms. Inc. v. Regeneron Pharms., Inc., IPR2021-00880, challenging claims of U.S. Patent No. 9,669,069 B2, Final Written Decision (Paper 89) issued Nov. 9, 2022;

Mylan Pharms. Inc. v. Regeneron Pharms. Inc., IPR2021-00881, challenging claims of U.S. Patent No. 9,254,338 B2, Final Written Decision (Paper 94) issued Nov. 9, 2022;

Mylan Pharms. Inc. v. Regeneron Pharms., Inc., IPR2022-01225, challenging claims of U.S. Patent No. 10,130,681 B2, Institution Decision (Paper 21) issued Jan. 11, 2023;

Samsung Bioepis Co. Ltd. v. Regeneron Pharms., Inc., IPR2023-00442, challenging claims of U.S. Patent No. 10,130,681 B2, petition filed Jan. 6, 2023;

Mylan Pharms. Inc. v. Regeneron Pharms., Inc., IPR2023-00099, challenging claims of U.S. Patent No. 10,857,205 B2, Decision Denying Institution (Paper 10) due to statutory disclaimer issued Mar. 1, 2023;

Mylan Pharms. Inc. v. Regeneron Pharms., Inc., IPR2022-01226, challenging claims of U.S. Patent No. 10,888,601 B2, Institution Decision (Paper 22) issued Jan. 11, 2023; and

Apotex, Inc. v. Regeneron Pharms., Inc., IPR2022-01524, challenging claims of U.S. Patent No. 11,253,572 B2, Decision Denying Institution (Paper 9) issued Mar. 10, 2023. *Id.*

Finally, Patent Owner lists the following pending applications as related to the '992 patent: U.S. Patent Application Nos. 17/072,417, 17/112,404, 17/112,063, and 17/350,958. *Id.*

C. The '992 Patent

The '992 patent is titled “VEGF Antagonist Formulations Suitable for Intravitreal Administration.” Ex. 1001, code (54). The '992 patent is directed to pharmaceutical formulations containing a vascular endothelial growth factor (“VEGF”) antagonist. *Id.* at 1:30–34. The '992 patent defines the term “VEGF antagonist” as a “compound capable of blocking or inhibiting the biological action of [VEGF], and includes fusion proteins capable of trapping VEGF.” *Id.* at 6:9–12. The '992 patent refers to such a fusion protein as a “VEGF trap” and discloses that it comprises “an

immunoglobulin-like (Ig) domain 2 of a first VEGF receptor and Ig domain 3 of a second VEGF receptor, and a multimerizing component.” *Id.* at 2:7–11. “In specific embodiments, the VEGF antagonist is expressed in a mammalian cell line such as a [Chinese Hamster Ovary (“CHO”)] cell and may be modified post-translationally.” *Id.* at 6:14–16.

According to the ’992 patent, “[p]roteins possess unique chemical and physical properties that present stability problems: a variety of degradation pathways exist for proteins, implicating both chemical and physical instability.” Ex. 1001, 5:37–40. In one embodiment, the ’992 patent describes “a stable pharmaceutically acceptable formulation comprising a VEGF antagonist.” *Id.* at 6:41–54. “The formulation can also comprise one or more pharmaceutically acceptable carriers, buffers, tonicity agents, stabilizers, and/or excipients.” *Id.* at 6:47–49. “An example of a pharmaceutically acceptable liquid formulation comprises a VEGF antagonist . . . , a buffer, an organic co-solvent such as polysorbate, a tonicity agent such as NaCl, and optionally, a stabilizer such as sucrose or trehalose.” *Id.* at 6:49–54.

The ’992 patent provides eight examples of VEGF Trap formulations and their corresponding stability test data. *See* Ex. 1001, 8:8–12:30. Examples 1–4 describe liquid formulations include varying amounts of VEGF Trap (SEQ ID NO: 4), phosphate, NaCl, polysorbate 20 or polyethylene glycol, and sucrose. *See id.* at 8:8–9:55. Examples 1–4 further disclose that the formulations contain at least 98% of VEGF Trap present in native configuration following storage at 5° C for two months as measured by size exclusion chromatography (“SEC”). *See id.*

D. Challenged Claims

Petitioner challenges claims 1–18 of the '992 patent. Pet. 1. Claims 1 and 10, which are the independent claims of the '992 patent, are illustrative of the challenged claims and are reproduced below, with the only difference being claim 1 describes a vial comprising a formulation and claim 10 describes the formulation.

1. A vial comprising:

a vascular endothelial growth factor (VEGF) antagonist,

an organic co-solvent,

a buffer, and

a stabilizing agent,

wherein the VEGF antagonist is a fusion protein produced in a Chinese Hamster Ovary (CHO) cell, the fusion protein comprising an immunoglobulin-like (Ig) domain 2 of a first VEGF receptor and Ig domain 3 of a second VEGF receptor, and a multimerizing component; and

wherein at least 98% of the VEGF antagonist is present in native conformation following storage at 5° C. for two months as measured by size exclusion chromatography.

Ex. 1001, 19:31–43.

10. A formulation comprising:

a vascular endothelial growth factor (VEGF) antagonist,

an organic co-solvent,

a buffer, and

a stabilizing agent,

wherein the VEGF antagonist is a fusion protein produced in a Chinese Hamster Ovary (CHO) cell, the fusion protein comprising an immunoglobulin-like (Ig) domain 2 of a first VEGF receptor and Ig domain 3 of a second VEGF receptor, and a multimerizing component; and

wherein at least 98% of the VEGF antagonist is present in native conformation following storage at 5° C. for two months as measured by size exclusion chromatography.

Id. at 19:65–20:40. Claims 2–9 and 11–18 depend from claims 1 and 10, either directly or indirectly.

E. The Asserted Grounds of Unpatentability

Petitioner asserts that claims 1–18 would have been unpatentable on the following grounds:

Ground	Claim(s) Challenged	35 U.S.C. § ¹	Reference(s)/Basis
1	1–18	102	Fraser ²
2	1–18	103	Fraser, Wulff ³ , Holash ⁴ , '319 Publication ⁵ , '309 Publication ⁶ , McNally

¹ The Leahy-Smith America Invents Act (“AIA”), Pub. L. No. 112–29, 125 Stat. 284 (2011), amended 35 U.S.C. § 103, was effective on March 16, 2013. Because the '992 patent claims priority to a provisional application that has a filing date before March 16, 2013, and Petitioner does not currently contest this priority date, we apply the pre-AIA version of § 103. We note that our analysis in this Decision would not change under AIA law.

² Fraser, Hamish M. et al., *Single Injections of Vascular Endothelial Growth Factor Trap Block Ovulation in the Macaque and Produce a Prolonged, Dose-Related Suppression of Ovarian Function*, J. Clin. Endocrinology & Metabolism, Vol. 90, No. 2, 1114–1122 (2005) (Ex. 1009, “Fraser”).

³ Wulff, Christine et al., *Prevention of Thecal Angiogenesis, Antral Follicular Growth, and Ovulation in the Primate by Treatment with Vascular Endothelial Growth Factor Trap R1R2*, Endocrinology, Vol. 143, No. 7, 2797–2807 (2002) (Ex. 1016, “Wulff”).

⁴ Holash, Jocelyn et al., *VEGF-Trap: A VEGF blocker with potent antitumor effects*, PNAS, Vol. 99, No. 17, 11393–11398 (2002) (Ex. 1010, “Holash”).

⁵ Papadopoulos et al., WO 00/75319 A1, published Dec. 14, 2000 (Ex. 1029, “the '319 publication”).

⁶ Kandel et al., US 2004/0265309 A1, published Dec. 30, 2004 (Ex. 1027, “the '309 publication”).

Ground	Claim(s) Challenged	35 U.S.C. § ¹	Reference(s)/Basis
			2000 ⁷ , FDA Guidance ⁸

Pet. 41. Petitioner submits the Declaration of Ralph Tarantino, R.Ph., Ph.D. (Ex. 1002) in support of institution of *inter partes* review. Patent Owner submits the Declarations of Alexander M. Klibanov, Ph.D. (Ex. 2001) and David M. Brown, M.D. (Ex. 2004).

F. Asserted Prior Art

1. Fraser (Ex. 1009)

Fraser, titled “Single Injections of Vascular Endothelial Growth Factor Trap Block Ovulation in the Macaque and Produce a Prolonged, Dose-Related Suppression of Ovarian Function,” describes a study that evaluated “a potent, receptor-based VEGF antagonist, the VEGF trap.” Ex. 1009, 1114. Specifically, Fraser describes administering VEGF Trap_{R1R2}, “a recombinant, chimeric protein comprising Ig domain 2 of human VEGF-R1 and Ig domain 3 of human VEGF-R2, expressed in sequence with the human [fragment crystallizable (Fc) region].” *Id.* at 1115. According to Fraser, “[c]ompared with earlier versions of receptor-based fusion proteins, the VEGF Trap_{R1R2} exhibits greater affinity for VEGF-A (affinity constant—1 pM) as well as improved bioavailability and pharmacokinetic properties.” *Id.* (citing Holash, Ex. 1010).

⁷ Paul McGoff & David S. Scher, *Solution Formulation of Proteins/Peptides* in PROTEIN FORMULATION AND DELIVERY vol. 99, 139–58 (Eugene J. McNally ed., 2000) (Ex. 1013, “McNally 2000”).

⁸ Food & Drug Administration, *Guidance for Industry, Container Closure Systems for Packaging Human Drugs and Biologics* (May 1999) (Ex. 1038, “FDA Guidance”).

Fraser further describes a formulation in which “VEGF Trap_{R1R2} (Regeneron Pharmaceuticals, Inc., Tarrytown, NY) was provided at a concentration of 24.3 mg/ml in 2-ml aliquots in buffer composed of 5 mM phosphate, 5 mM citrate, 100 mM NaCl (pH 6.0), and 0.1% wt/vol Tween 20, with either 20% glycerol or 20% sucrose.” Ex. 1009, 1115. “The compounds were stored at -20 C until required, at which time they were thawed. Any compound remaining was stored at 4 C and used within 2 wk.” *Id.*

2. *Dix (Ex. 1021)*⁹

Dix, titled “VEGF Antagonist Formulations,” describes a stable liquid formulation including a VEGF-specific fusion protein antagonist. Ex. 1021, codes (54), (57). Dix refers to the antagonist as a “VEGF ‘trap’” that comprises “a receptor component consisting essentially of an immunoglobulin-like (Ig) domain 2 of a first VEGF receptor and Ig domain 3 of a second VEGF receptor, and a multimerizing component.” *Id.* at 1:43–54. Dix provides several examples of formulations including VEGF trap (SEQ ID NO: 4). *See id.* at 7:7–12:20. In one embodiment, the formulation contains “about 5 mM phosphate, 5 mM citrate, 100 mM NaCl, 0.1% polysorbate 20, 20% sucrose, and 25 mg/ml VEGF trap protein.” *Id.* at 11:15–20. The formulation is characterized by a pH ranging from 6.0–6.1. *Id.* Stability testing over 36 months at 5° C provided the following results:

⁹ Dix et al., US 8,110,546 B2, issued Feb. 7, 2012 (Ex. 1021, “Dix”). Petitioner relies on Dix as evidence “that the claimed level of stability is the natural result of the ingredients in the *Fraser* formulation.” *See* Pet. 47.

TABLE 9

Stability and Activity of Liquid Formulation (VEGF-ES405)				
Months	% Native Configuration	Bioassay	Binding Assay	Protein Content mg/ml
0	99.7	106	72	25.0
1	99.9	119	4.4 pM*	25.2
2	99.6	102	5.4 pM*	25.1
3	99.6	97	88	25.1
6	99.6	101	106	25.0
9	99.4	89	136	25.4
12	99.5	85	95	25.2
18	99.4	99	81	25.5
24	99.3	75	95	25.6
36	98.8	109	79	25.6

Id. at 12:5–20.

3. *Wulff (Ex. 1016)*

Wulff, titled “Prevention of Thecal Angiogenesis, Antral Follicular Growth, and Ovulation in the Primate by Treatment with Vascular Endothelial Growth Factor Trap R1R2,” describes a study that evaluated the anti-angiogenic properties of VEGF Trap R1R2. Ex. 1016, 2797. Wulff describes “VEGF Trap R1R2 used in these experiments [as] a recombinant chimeric protein comprising portions of the extracellular, ligand binding domains of the human VEGF receptors Flt-1 (VEGF-R1, Ig domain 2) and KDR (VEGF-R2, Ig domain 3) expressed in sequence with the Fc portion of human [immunoglobulin G (IgG)].” *Id.* at 2798, Fig. 1.

Figure 1 is reproduced below:

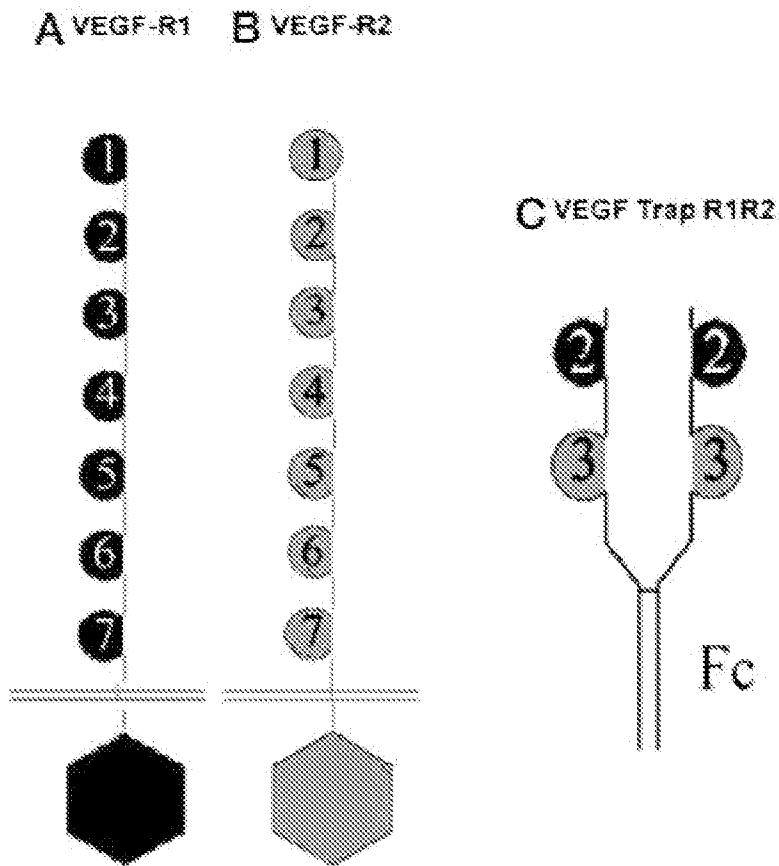


Figure 1A and 1B illustrates VEGF receptors R1 and R2, respectively. Ex. 1016, 2798. VEGF-R1 and VEGF-R2 are each illustrated as a line extending from an intracellular domain (filled hexagon), across a cell membrane (double-line), to seven extracellular domains individually illustrated as numbered circles on the line. *See id.* “These extracellular domains are responsible for VEGF binding.” *Id.* Figure 1C illustrates VEGF Trap R1R2 as including the Fc portion of IgG with two extending arms, each including domain 2 of VEGF-R1 and domain 3 of VEGF-R2 shown as circles numbered 2 and 3, respectively. *See id.*

Wulff discloses that “[t]he presence of the Fc domain results in homodimerization of the recombinant protein, thereby creating a high affinity (KD1-5pM) VEGF Trap.” Ex. 1016, 2798. Wulff further discloses that “the detailed molecular structure” of the VEGF Trap is described in the

PCT Publication WO 00/75319 A1 (the '319 application) (Ex. 1029). *Id.* at 2798 n.1. Additionally, according to Wulff, “[t]he VEGF trap was expressed in CHO cells and was purified by protein A affinity chromatography followed by size-exclusion chromatography.” *Id.* at 2798.

4. *Holash (Ex. 1010)*

Holash is titled “VEGF-Trap: A VEGF blocker with potent antitumor effects.” Ex. 1010, 11393. Holash describes engineering VEGF Traps. *Id.* Specifically, Holash describes the following process:

The parental VEGF-Trap was created by fusing the first three Ig domains of VEGF_{R1} to the constant region (Fc) of human IgG1. VEGF-Trap_{ΔB1} was created by removing a highly basic 10-aa stretch from the third Ig domain of the parental VEGF-Trap. VEGF-Trap_{ΔB2}, was created by removing the entire first Ig domain from VEGF-Trap_{ΔB1}. VEGF-Trap_{R1R2} was created by fusing the second Ig domain of VEGFR1 with the third Ig domain of VEGFR2. All of these VEGF-Trap variants were produced and purified from Chinese hamster ovary cells.

Id. at 11393–11394.

5. *The '309 publication (Ex. 1027)*

The '309 publication, titled “Method of Tumor Regression with VEGF Inhibitors,” relates to methods of administering a VEGF blocker to reduce tumor size and inhibit tumor metastases. Ex. 1027, codes (54), (57). The '309 publication states that, in a “preferred embodiment, the VEGF trap is VEGFR1R2-FcΔC1(a) (also termed VEGF trap_{R1R2}) having the nucleotide sequence set forth in SEQ ID NO: 1 and the amino acid sequence set forth in SEQ ID NO: 2.” *Id.* ¶¶ 5, 22. It also states, “[f]or a complete description of VEGF-receptor based antagonists including VEGFR1R2- FcΔC1(a), see PCT publication WO/00/75319, the contents of which is herein incorporated by reference in its entirety.” *Id.* ¶ 22.

6. *The '319 publication (Ex. 1029)*

The '319 publication, titled “Modified Chimeric Polypeptides with Improved Pharmacokinetic Properties,” relates to VEGF antagonists. Ex. 1029, code (54), 10:3–14. More specifically, the '319 publication describes VEGF antagonists including a VEGF receptor component linked to a multimerizing component. *Id.* at 10:3–14. The VEGF receptor component includes Ig domain 2 of the extracellular domain of a first VEGF receptor and Ig domain 3 of the extracellular domain of a second VEGF receptor. *Id.* The '319 publication further describes a host-vector system for producing the fusion polypeptide, wherein a CHO cell is the host cell. *Id.* at 12:19–26.

7. *McNally 2000 (Ex. 1013)*

McNally 2000 is titled “Solution Formulation of Proteins/Peptides.” Ex. 1013, 139. McNally 2000 explains that “[t]he simplest and most economical way to formulate a protein is to develop a solution formulation.” *Id.* According to McNally, a formulation scientist can determine whether a solution formulation will be acceptable for a given protein. *Id.* The scientist can use initial formulation studies to identify problems such as poor solubility or aggregation. *See id.* “For example, a particular pH or mix of buffer components used during processing may reduce solubility or induce aggregation.” *Id.* at 139–140.

McNally 2000 further describes analytical test procedures for characterizing the physicochemical properties of the protein. Ex. 1013, 140. Typical properties monitored include conformation and size using size exclusion chromatography (SEC). *Id.*

McNally provides a “step-by-step[] how-to protocol” for a protein solution formulation development study. Ex. 1013, 156–157. “Ideally, the

protein concentration and solubility are determined first to establish a working range for the initial pH stability study.” *Id.* at 156. “The next phase of experiments should focus on a narrower pH and concentration range and should study higher temperatures, possibly adding stabilizing excipients and extending the time frame of the study to at least one year. *Id.* at 157. “Specific buffer ion effects could be investigated during this phase.” *Id.*

8. *FDA Guidance (Ex. 1038)*

FDA Guidance is titled “Guidance for Industry, Container Closure Systems for Packaging Human Drugs and Biologics.” Ex. 1038. The Guidance provides general principles for submitting information on packaging materials used for human drugs and biologics. *Id.* at 1. The FDA Guidance explains that “[i]njectable dosage forms represent one of the highest risk drug products” because “[a]ny contaminants present . . . can be rapidly and completely introduced into the patient’s general circulation. *Id.* at 23–24. Injectable products, whether small-volume or large-volume parenterals, may be packaged in vials. *Id.*

III. DENIAL UNDER 35 U.S.C. § 325(d)

Patent Owner asserts that we should deny the Petition under 35 U.S.C. § 325(d) because the Petition presents substantially the same art and arguments that the Office previously analyzed and fails to show that the Office erred during prosecution. *See* Prelim. Resp. 58–68.

We have discretion to deny review when “the same or substantially the same prior art or arguments previously were presented to the Office.” 35 U.S.C. § 325(d) (“Section 325(d)”). In that respect, Section 325(d) provides that the Director may elect not to institute a proceeding if the challenge to the patent is based on matters previously presented to the

Office.¹⁰ *Advanced Bionics, LLC v. Med-El Elektromedizinische Geräte GmbH*, IPR2019-01469, Paper 6 at 7 (PTAB Feb. 13, 2020) (precedential) (“*Advanced Bionics*”).

In evaluating the exercise of discretion to deny institution under Section 325(d), the Board uses the following two-part framework: (1) determining whether the same or substantially the same art previously was presented to the Office or whether the same or substantially the same arguments previously were presented to the Office; and (2) if either condition of the first part of the framework is satisfied, determining whether the petitioner has demonstrated that the Office erred in a manner material to the patentability of challenged claims. *Advanced Bionics*, Paper 6 at 8.

In applying the two-part framework, we consider several non-exclusive factors, including:

- (a) the similarities and material differences between the asserted art and the prior art involved during examination;
- (b) the cumulative nature of the asserted art and the prior art evaluated during examination;
- (c) the extent to which the asserted art was evaluated during examination, including whether the prior art was the basis for rejection;
- (d) the extent of the overlap between the arguments made during examination and the manner in which petitioner relies on the prior art or patent owner distinguishes the prior art;
- (e) whether petitioner has pointed out sufficiently how the examiner erred in its evaluation of the asserted prior art; and
- (f) the extent to which additional evidence and facts presented in the petition warrant reconsideration of the prior art or arguments.

¹⁰ The Board institutes trial on behalf of the Director. 37 C.F.R. § 42.4(a).

Becton, Dickinson & Co. v. B. Braun Melsungen AG, IPR2017-01586, Paper 8 at 17–18 (PTAB Dec. 15, 2017) (precedential as to Section III.C.5, first paragraph) (“*Becton, Dickinson*”).

Factors (a), (b), and (d) relate to whether the art or arguments presented in the Petition are the same or substantially the same as those previously presented to the Office. *Advanced Bionics*, Paper 6 at 10. Factors (c), (e), and (f) “relate to whether the petitioner has demonstrated a material error by the Office” in its prior consideration of that art or arguments. *Id.* Only if the same or substantially the same art or arguments were previously presented to the Office do we then consider whether petitioner has demonstrated a material error by the Office. *Id.*

A. The ’992 Patent Prosecution History

The original application for the ’992 patent was filed with a preliminary amendment cancelling claims 1–11 and listing new claims 12–29. Ex. 1004, 2–4.¹¹ Claims 12 and 21 were identical to now-issued claims 1 and 10, except that they lacked the last clause of the claims reciting the presence of at least 98% of the VEGF antagonist in native conformation following storage. *See id.*

In a Non-Final Action dated April 2, 2019, the Examiner rejected claims 12–29 for nonstatutory double patenting. Ex. 1004, 74–79. Specifically, the Examiner rejected claims 12–29 as being unpatentable over claims 1–7 and 11–17 of U.S. Patent No. 8,092,803 (“the ’803 patent”), claims of other related patents, and claims 12–26 of co-pending Application No. 15/879,294. *See id.* at 77–79.

¹¹ The cited page numbers in Exhibit 1004 refer to the page numbers added by Petitioner in the bottom-right corner of the page.

In response, the applicant amended pending claims 12 and 21 to recite the native conformation limitation recited by now-issued claims 1 and 10, respectively. Ex. 1004, 90–91. The applicant filed a terminal disclaimer as to the '803 patent. *See id.* at 93, 96. The applicant argued that the amended claims were patentably distinct from the other patents and application asserted in the double-patenting rejection. *See id.* at 93–94. Specifically, the applicant argued that “[i]ndependent claims 12 and 21 have been amended to include an element relating to the stability of the protein conformation in storage over a period of time. This element is not contained within any of the claims” asserted by the Examiner in the double-patenting rejection, excluding the '803 patent. *Id.* Following the amendment and terminal disclaimer, the Examiner allowed the claims. *Id.* at 104–111.

B. Same or Substantially the Same Art or Arguments Previously Presented to the Office

We first consider whether Petitioner asserts the same or substantially the same art or arguments that previously were presented to the Office. *Advanced Bionics*, Paper 6 at 8. Patent Owner contends that “Petitioner’s primary reference for both Grounds 1 and 2, Fraser (Ex.1009), was cited in an [Information Disclosure Statement (‘IDS’)] during prosecution of the application that resulted in the '992 patent. The Examiner signed the IDS as considered and thus is presumed to have considered it.” Prelim. Resp. 53 (citing *Husky Injection Molding Systems, Ltd., et al., v. Plastipak Packaging, Inc.*, IPR2020-00428, Paper 24 at 11 (PTAB July 28, 2020)). Patent Owner also contends that Holash was presented to the Patent Office because “Holash (Ex.1010) is expressly cited in the specification of the '992 patent and incorporated by reference in its entirety.” *Id.* at 54 (citing Ex. 1001, 1:50–52).

Patent Owner further argues that we should find Petitioner's additional references to be substantially the same as art that was presented to the Office. *See* Prelim. Resp. 54–60. First, Patent Owner contends that WO 2006/104852 (Ex. 2022) and U.S. Patent Publication No. 2006/0217311 (Ex. 2023), which were provided to the Examiner during prosecution, include the same data as in the Dix patent on which Petitioner relies. *Id.* at 54–56 (citing Ex. 1001, code (56); Ex. 1004, 87; Ex. 2022; Ex. 2023). Patent Owner also contends that Wulff is cumulative to Fraser (disclosing “the effects of a VEGF antagonist on the reproductive system of primates”) and Holash (disclosing “using CHO cells to produce the VEGF antagonist”). *See id.* at 56–57.

Additionally, Patent Owner contends that “both Wulff (Ex.1016) and the '319 Publication (Ex.1029) were considered during prosecution of a continuation application filed by Patent Owner, Ex.2024; Ex.2025, which issued as U.S. Patent No. 11,066,458 [“the '458 patent”], Ex.2026.” Prelim. Resp. 57. Patent Owner further contends that the relevant disclosures of the '309 Publication are cumulative of the '319 Publication, which was before the Patent Office during the prosecution of the '458 patent. *Id.* at 58.

Finally, Patent Owner contends that McNally 2000 and FDA Guidance “both simply describe general knowledge of the POSA.” Prelim. Resp. 59. “Patent Owner does not dispute that these two references would have been part of the general knowledge of a POSA.” *Id.*

Petitioner asserts that the “petition presents art and arguments that are materially different than those presented to the Office during prosecution of the '992 patent” and that the only rejections made during prosecution of the

application that led to the '992 patent were obviousness-type double-patenting rejections. Pet. 33.

Petitioner further argues that the prosecution of the prior applications in the patent family indicates that the Examiner did not consider the cited references. *See* Pet. 33–34. Specifically, Petitioner asserts that “[t]he prosecution histories of these applications do not contain any rejections over the prior art. Rather, the claims in the priority application were rejected only for obviousness-type double patenting, written description, and indefiniteness.” *Id.* (citing Exs. 1039–1046). Petitioner contends that “reviewing the prosecution of all of the priority applications, in which no rejections over the prior art were made, but rather the claims were rejected for obviousness-type double patenting, it is apparent that the Examiner did not consider the *Fraser* reference.” *Id.* at 34.

Finally, Petitioner argues that the Petition “raises new arguments about *Fraser* not before the Office during prosecution that are based on new evidence and prior art that were not before the Office during prosecution.” Pet. 35. For example, Petitioner argues that “the '319 *Publication* or the '309 *Publication*, [disclose] that the VEGF Trap_{R1R2} protein in the *Fraser* formulation is aflibercept.” *Id.* Petitioner argues that Wulff discloses “that Regeneron’s VEGF Trap_{R1R2} protein was made using CHO cells.” *Id.* And Petitioner argues that Dix discloses that “Patent Owner’s own tests established that the *Fraser* formulation met (and indeed exceeded) the 99% native conformation limitation of the challenged claims.” *Id.*

We agree with Patent Owner that *Fraser* was cited during prosecution of the application that led to the '992 patent and was, therefore, previously presented to the Office. *Advanced Bionics*, Paper 6 at 7–8 (“Previously presented art includes art made of record by the Examiner, and art provided

to the Office by an applicant, such as on an [IDS], in the prosecution history of the challenged patent.”); Ex. 1004, 87. Because Fraser is Petitioner’s sole reference for Ground 1, and primary reference for Ground 2, we, therefore, find that the same or substantially the same art was previously presented regardless of whether the other references are cumulative of ones that were presented during prosecution.

C. Whether the Office Erred in a Manner Material to Patentability

Because we find that the same or substantially the same art previously was presented to the Office, we turn to whether Petitioner demonstrates that the Office erred in a manner material to the patentability of the challenged claims. *Advanced Bionics*, Paper 6 at 8, 10; *see Becton, Dickinson*, Paper 8 at 24.

Petitioner contends that “through no fault of the examiner, the Office erred to any extent it evaluated *Fraser*.” Pet. 36. Petitioner also argues that the petition “raises new arguments about *Fraser* not before the Office during prosecution that are based on new evidence” and explains how the Examiner erred in failing to apply Fraser against the claims. *Id.* at 35–36.

Patent Owner contends that Petitioner has not established error with respect to Fraser and that “Petitioner does not allege material error by the Patent Office with respect to any of [the] other key prior art, and there is none.” Prelim. Resp. 62.

We find that Petitioner has sufficiently shown error in this case. As discussed further below with respect to the Grounds, the Petition establishes that the VEGF Trap_{R1R2}¹² protein disclosed in Fraser is the same as the one

¹² The term “VEGF Trap_{R1R2}” is denoted as “VEGF Trap_{R1R2},” “VEGFTrap_{R1R2}” and “VEGF trap_{R1R2}” in the briefing and references. Petitioner also uses the term “aflibercept” interchangeably with these terms.

disclosed in the Dix publication. Petitioner has also shown that Fraser’s VEGF Trap_{R1R2} formulation is the same as that disclosed in Dix, which establishes that the Fraser formulation meets the 98% native conformation limitation of the challenged claims. We, therefore, find that the Petitioner demonstrates that the Examiner misapprehended or overlooked the teachings of Fraser in this regard, and we decline to exercise our discretion to deny institution under 35 U.S.C. § 325(d).

IV. ANALYSIS

A. *Person of Ordinary Skill in the Art*

“The level of skill in the art is a factual determination” that provides a primary guarantee of objectivity in an obviousness analysis. *Al-Site Corp. v. VSI Int’l Inc.*, 174 F.3d 1308, 1324 (Fed. Cir. 1999) (citing *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966); *Ryko Mfg. Co. v. Nu-Star, Inc.*, 950 F.2d 714, 718 (Fed. Cir. 1991)).

Petitioner asserts that a person of ordinary skill in the art (“POSA”) at the time of the invention “would have had a Ph.D. in pharmaceutical sciences or a similar field, with at least several years of experience in the development, manufacture and characterization of formulations of therapeutic proteins, including, for example, fusion proteins or antibodies.” Pet. 30 (citing Ex. 1002 ¶¶ 39–43). Petitioner further asserts that the POSA “would have understood how to combine proteins with compatible excipients such as surfactants, stabilizers, salts and buffers of various pH values, and how to adjust these combinations in order to optimize their stability in liquid or solid form.” *Id.* at 30–31. Petitioner asserts that the

Because Fraser uses the term “VEGF Trap_{R1R2}” (Ex. 1009, 1115), we use the same nomenclature in this Decision.

POSA would have been able to assess stability and compatibility by using “state-of-the-art analytical methods, such as SEC.” *Id.* at 31.

Patent Owner does not contest the characterization offered by Petitioner. *See* Prelim. Resp. 16.

For purposes of this Decision, we adopt Petitioner’s characterization because it is consistent with the level of skill in the art at the time of the invention as reflected by the ’992 patent and the cited prior art. *See Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001) (explaining that specific findings regarding ordinary skill level are not required “where the prior art itself reflects an appropriate level and a need for testimony is not shown” (quoting *Litton Indus. Prods., Inc. v. Solid State Sys. Corp.*, 755 F.2d 158, 163 (Fed. Cir. 1985))).

B. Claim Construction

We interpret a claim “using the same claim construction standard that would be used to construe the claim in a civil action under 35 U.S.C. 282(b).” 37 C.F.R. § 42.100(b) (2019). Under this standard, we construe the claim “in accordance with the ordinary and customary meaning of such claim as understood by one of ordinary skill in the art and the prosecution history pertaining to the patent.” *Id.*

Petitioner proposes claim construction for three terms under their plain and ordinary meaning. *See* Pet. 41–42. First, Petitioner asserts that the “POSA would have understood that the term ‘native’ in the phrase ‘native conformation’ in claims 1, 2, 10 and 11 refers to the fully intact and functional conformation of the protein.” *Id.* at 42 (citing Ex. 1002 ¶ 22). Second, Petitioner asserts that the “POSA would have understood the term ‘vial’ in claims 1–9 to refer to a small closed or closable vessel, especially for liquids.” *Id.* (citing Ex. 1031; Ex. 1002 ¶¶ 23, 190). Third, Petitioner

asserts that the “[t]he POSA would have understood the term ‘multimerizing component’ in claims 1 and 10 to refer to a protein moiety that joins two or more protein domains together to form a multimer, such as a dimer or trimer.” *Id.* (citing Ex. 1002 ¶ 24). Patent Owner does not challenge Petitioner’s proposed claim constructions. Prelim. Resp. 16.

For purposes of this Decision, however, we determine that no claim terms require express construction. *See Nidec Motor Corp. v. Zhongshan Broad Ocean Motor Co.*, 868 F.3d 1013, 1017 (Fed. Cir. 2017) (citing *Vivid Techs., Inc. v. Am. Sci. & Eng’g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999) (“[O]nly those terms need be construed that are in controversy, and only to the extent necessary to resolve the controversy.”)).

C. Asserted Anticipation of Claims 1–18 by Fraser

Petitioner contends that claims 1–18 are anticipated by Fraser. Pet. 42–53. Patent Owner disputes Petitioner’s contentions. Prelim. Resp. 16–44.

1. Principles of Law

To establish anticipation under 35 U.S.C. § 102, each and every element in a claim, arranged as recited in the claim, must be found in a single prior art reference. *Net MoneyIN, Inc. v. VeriSign, Inc.*, 545 F.3d 1359, 1369 (Fed. Cir. 2008); *Karsten Mfg. Corp. v. Cleveland Golf Co.*, 242 F.3d 1376, 1383 (Fed. Cir. 2001). Each element of the challenged claim must be found, either expressly or inherently, in the single prior art reference. *Verdegaal Bros., Inc. v. Union Oil Co. of Cal.*, 814 F.2d 628, 631 (Fed. Cir. 1987). When evaluating a prior art reference in the context of anticipation, the reference must be “considered together with the knowledge of one of ordinary skill in the pertinent art.” *In re Paulsen*, 30 F.3d 1475, 1480 (Fed. Cir. 1994) (citing *In re Samour*, 571 F.2d 559, 562 (CCPA

1978)). “[A] reference can anticipate a claim even if it ‘d[oes] not expressly spell out’ all the limitations arranged or combined as in the claim, if a person of skill in the art, reading the reference, would ‘at once envisage’ the claimed arrangement or combination.” *Kennametal, Inc. v. Ingersoll Cutting Tool Co.*, 780 F.3d 1376, 1381 (Fed. Cir. 2015) (quoting *In re Petering*, 301 F.2d 676, 681 (CCPA 1962)).

2. *Petitioner’s Position*

Petitioner contends that Fraser discloses a formulation comprising a VEGF antagonist, specifically VEGF Trap_{R1R2}. Pet. 43 (citing Ex. 1009, 1115; Ex. 1002 ¶ 90). According to Petitioner, VEGF Trap_{R1R2} is a fusion protein comprising Ig domain 2 of VEGF-R1, Ig domain 3 of VEGF-R2, and human Fc, a multimerizing component. *Id.* (citing Ex. 1009, 1115). Petitioner contends that Fraser further discloses that the formulation includes an organic co-solvent, i.e., Tween 20 (polysorbate 20); buffer, i.e., phosphate, citrate, and NaCl (pH 6.0); and a stabilizing agent, i.e., glycerol or sucrose. *Id.* at 44–45 (citing Ex. 1009, 1115; Ex. 1002 ¶¶ 73, 91–92). As to claim 1 specifically, Petitioner contends that “[t]he *Fraser* formulation was necessarily present in a ‘vial’ and a POSA reading *Fraser* would have understood this.” *Id.* at 48–50 (citing Ex. 1002 ¶¶ 104–113).

Petitioner notes that Fraser states that the VEGF Trap_{R1R2} formulation contained either 20% glycerol or 20% sucrose, but cites to Regeneron’s prosecution statements and lab notebooks as indicating that the Fraser formulation contained 20% sucrose. Pet. 45 (citing Ex. 1022, Exhibit C; Ex. 1023, 2). Petitioner also contends that a POSA would have understood that Fraser’s VEGF Trap_{R1R2} was produced in CHO cells. *Id.* Specifically, Petitioner contends that Fraser’s VEGF Trap_{R1R2} “‘was provided’ by Regeneron,” and Fraser references Holash to describe the properties of

VEGF Trap_{R1R2}. *Id.* (citing Ex. 1009, 1115). According to Petitioner, Holash discloses that VEGF Trap_{R1R2} was produced and purified from CHO cells. *Id.* (citing Ex. 1010, 11393–11394). Petitioner asserts that Fraser’s reference to VEGF Trap_{R1R2} being “provided” by Regeneron and the disclosure of Holash “would have informed a POSA that the VEGF Trap_{R1R2} in *Fraser* was produced in CHO cells.” *Id.* at 45–46 (citing Ex. 1002 ¶¶ 93–95). Similarly, Petitioner asserts that Wulff, the ’319 publication, and the ’309 publication also confirm that Fraser’s VEGF Trap_{R1R2} protein was produced in CHO cells. *See id.* at 46 (citing Ex. 1016, 2798; Ex. 1027 ¶ 26; Ex. 1029, Example 21; Ex. 1002 ¶¶ 93–95).

Petitioner acknowledges that Fraser does not disclose that at least 98% of VEGF Trap_{R1R2} in the formulation is present in native conformation after storage at 5° C for two months. *See* Pet. 46. However, Petitioner argues that “the stability of the *Fraser* formulation is the natural result of its ingredients.” *Id.* (citing Ex. 1002 ¶¶ 96–102). First, Petitioner contends that “[t]he fact that the *Fraser* formulation has the same ingredients as the claimed formulation is enough to establish a *prima facie* case of anticipation,” *Id.* at 46–47 (citing *In re Best*, 562 F.2d 1252, 1255 (CCPA 1977)). Second, Petitioner asserts that “[a]nother Regeneron publication, *Dix*, published after the priority date, disclosed that Regeneron conducted stability testing on the same formulation and found that greater than 99% of the aflibercept remained in native conformation as measured by SEC after storage for 2 months at 5 °C.” *Id.* at 47–48 (citing Ex. 1002 ¶¶ 96–102; Ex. 1021, 11:15–12:20, Table 9; Ex. 1002 ¶¶ 97, 100).

3. Patent Owner’s Position

Patent Owner raises two main arguments. First, Patent Owner contends that Petitioner has not shown that Fraser’s formulation meets the

“native conformation limitation.” *See* Prelim. Resp. 16–41. Second, Patent Owner contends that Petitioner has not shown that Fraser’s fusion protein was created in CHO cells. *See id.* at 41–44.

Patent Owner’s first argument seeks to distinguish Fraser’s VEGF Trap_{R1R2} from Dix’s VEGF trap protein (amino acid SEQ ID NO:4), so that Petitioner cannot rely on Dix’s stability data for inherency. *See* Prelim. Resp. 16–18; *see* Sur-Reply 1–3. Patent Owner argues that “Fraser and Wulff set forth the broad structural characteristics needed to qualify as a ‘VEGFTrap_{R1R2}’ or ‘R1R2,’ which is a genus of fusion proteins, not a single molecule.” Prelim. Resp. 19 (citing Ex. 2001 ¶¶ 39–43). Patent Owner also argues that the ’319 publication supports this contention by disclosing that two R1R2 fusion proteins, Flt1.D2.Flk1D3.FcΔC1(a) and VEGFR1R2-FcΔC1(a), “are distinct fusion proteins, with distinct amino acid sequences.” *Id.* at 20–25 (citing Ex. 1029, 21:16–17, 22:1–2, 51:5–12, 58:22–59:10, 61:2–8, 67:4–15, Figures 21A–21C, 24A–24C; Ex. 2001 ¶¶ 46–50, 53–61, 63–65).

According to Patent Owner, for the same reasons, the ’319 publication and the ’309 publication do not establish “that Fraser or Wulff used ‘VEGF-Trap_{R1R2}’ or similar terms to refer to—and only to—aflibercept.”¹³ Prelim. Resp. 35–37; *see* Sur-Reply 5. Finally, Patent Owner argues that Petitioner cannot use Patent Owner’s “post-priority statements” to show that Fraser’s VEGF Trap_{R1R2} is the same as Dix’s protein. *See* Prelim. Resp. 32–35.

¹³ In response to these arguments, Petitioner contends that the VEGF Trap_{R1R2} protein, disclosed by Fraser, Wulff, and Holash, and VEGFR1R2-FcΔC1(a), disclosed by the ’309 publication, all refer to the same protein, “aflibercept” and that Patent Owner has previously referred to VEGF Trap_{R1R2}, described in Holash, as aflibercept. *See* Reply 1–4; Pet. 14 n.1 (citing Ex. 1020, 2, 6–7; Ex. 1002 ¶ 64).

According to Patent Owner, their statement to the Office that “[t]he name of the active ingredient of EYLEA™ is aflibercept, also known as VEGF trap, VEGF-trap, VEGF Trap-Eye and VEGF-TRAP_{R1R2},” merely indicates that “aflibercept may sometimes be referred to by the name of the genus to which it belongs” *Id.* at 32–33. Patent Owner further argues, that as a matter of law, “Patent Owner’s post-priority date statements cannot be relied upon to ‘fill in’ missing disclosures in the prior art.” *Id.* at 34; *see* Sur-Reply 3–4 (citing *Endo Pharms. Sols., Inc. v. Custopharm, Inc.*, 894 F.3d 1374, 1383 (Fed. Cir. 2018) (“*Endo*”)).

Separately from arguing that Fraser does not disclose the same fusion protein as Dix, Patent Owner also argues that neither Fraser nor Wulff discloses the same formulation as Dix. *See* Prelim. Resp. 37–41. Patent Owner contends that “Fraser does not make clear that it used ‘20% sucrose’ as a stabilizer, as Dix did.” *Id.* Thus, Patent Owner contends that one cannot assume “that the data disclosed in Dix applies to the formulation used in Fraser when Petitioner fails to show that both references used the same formulation.” *Id.* Patent Owner further argues that Petitioner’s expert concedes that Fraser’s formulation and Dix’s formulation have different lot numbers, “suggesting that the proteins and/or formulations are *not* the same.” *Id.* at 28 (citing Ex. 1002 ¶ 101 n.6).

Patent Owner’s second main argument is that Petitioner fails to demonstrate that Fraser’s VEGF Trap_{R1R2} was necessarily created in CHO cells. *See* Prelim. Resp. 41–44. Patent Owner argues that Fraser’s reference to Holash does not indicate that the same VEGF Trap_{R1R2} from Holash was used by Fraser or that Holash’s host cell applies to Fraser but, rather, Holash is cited for other properties of VEGF Trap_{R1R2}. *See id.* at 41–43 (citing Pet. 45; Ex. 1009, 1115; Ex. 1017, 1393).

With regard to the disclosure of Wulff, Patent Owner argues that “[w]hether Wulff might cause a POSA to speculate that perhaps CHO cells were used to produce the Fraser protein is not relevant to whether Petitioner has shown that Fraser *anticipates* the challenged claims.” Prelim. Resp. 43–44. Accordingly, Patent Owner contends that “Petitioner thus has not met its burden to show that Fraser discloses that the particular VEGF Trap_{R1R2} protein used therein was produced in CHO cells.” *Id.* at 44.

4. Analysis

We first address Patent Owner’s argument that Petitioner has failed to show that Fraser discloses the same protein as in Dix (SEQ ID NO:4) because Dix refers to a specific protein while Fraser refers to a genus of proteins. Prelim. Resp. 18–37.

We agree with Petitioner that Fraser discloses VEGF Trap_{R1R2} as a specific protein molecule, describing it as “a recombinant, chimeric *protein*” that is “a *successor molecule*” to Patent Owner’s earlier VEGTrap_{A40}. Reply 1–2 (citing Ex. 1009, 1114–15). Fraser refers to the protein as “*the* VEGF Trap_{R1R2}” and reports its specific physical, pharmacokinetic, and pharmacodynamic properties. *Id.* at 2 (citing Ex. 1009, 1115). The ’309 publication also indicates that VEGF Trap_{R1R2} is a particular protein having a specific amino acid sequence. Ex. 1027 ¶ 5 (“In a specific and preferred embodiment, the VEGF trap is VEGFR1R2-FcΔC1(a) (also termed VEGF trap_{R1R2}) having the nucleotide sequence set forth in SEQ ID NO: 1 and the amino acid sequence set forth in SEQ ID NO: 2”).¹⁴

¹⁴ Petitioner represents that the amino acid sequence from the ’309 publication is the same as the one disclosed in Dix as well as other Regeneron publications. *See* Pet. 14–15, 24–25, 47–48 (citing Ex. 1002 ¶¶ 64, 65, 97; Ex. 1029, 12, 15, Fig. 24A–24C; Ex. 1028 ¶ 8. SEQ ID Nos. 3

We further agree with Petitioner that Wulff discloses “[t]he VEGF Trap_{R1R2} used in [its] experiments” as a single protein with a specific structure. Reply 2 (citing Ex. 1016, 2798) (alterations in original). Wulff discloses that “VEGF Trap_{R1R2}” was a “new compound” and “a recombinant chimeric protein” and that the “detailed molecular structure” of the protein “and how it was created” was described in the ’319 publication. Ex. 1016, 2797–98, 2798 n.1, 2804.

We are not persuaded by Patent Owner’s argument that the ’319 publication supports its assertion that the protein disclosed in Fraser is a genus of proteins because the ’319 publication discloses that two R1R2 fusion proteins, Flt1.D2.Flk1D3.FcΔC1(a) and VEGFR1R2-FcΔC1(a), “are distinct fusion proteins, with distinct amino acid sequences.” Prelim. Resp. 20–25. The ’319 publication refers to these two proteins as two “R1R2” proteins, not as two “VEGF Trap_{R1R2}” proteins. Patent Owner does not cite to any references in which the term, “VEGF Trap_{R1R2},” is used to refer to more than one protein. Thus, we find that, on the current record, Petitioner has sufficiently shown that the VEGF Trap_{R1R2} protein disclosed in Fraser is a specific protein having the same amino acid sequence as the protein disclosed in Dix.

We further find that Petitioner has shown that Fraser discloses the claimed formulation. On the current record, Petitioner sufficiently demonstrates that Fraser’s VEGF Trap_{R1R2} formulation includes an organic co-solvent, i.e., Tween 20 (polysorbate 20); buffer, i.e., phosphate, citrate,

and 4; Ex. 1019, 10:15–17, Figs. 24A–24C; Ex. 1019, 10:15–17, Figs. 24A–24C; Ex. 1020, 6–7; Ex. 1021, 11:15–12:20, Table 9). Patent Owner does not contest this representation.

and NaCl (pH 6.0); and a stabilizing agent, i.e., glycerol or sucrose.
Ex. 1009, 1115; Ex. 1002 ¶¶ 73, 91–92.

Patent Owner asserts that Petitioner has not shown that Fraser discloses the same formulation as Dix because “Fraser does not make clear that it used ‘20% sucrose’ as a stabilizer, as Dix did.” Prelim. Resp. 37–41. Fraser discloses that the formulation includes “either 20% glycerol or 20% sucrose.” Ex. 1009, 1115. Petitioner cites to lab notebook pages and statements made by Patent Owner during patent prosecution to show that Fraser used 20% glucose in its formulation. *See* Pet. 45 (citing Ex. 1023, 2). Specifically, during prosecution of Dix, Patent Owner submitted lab notebook pages showing the “actual lot and formulation used in Fraser,” which included “20% sucrose.” Ex. 1023, 2 (citing Ex. 1022, Exhibit C). Petitioner also cites to Wulff, which discloses use of a VEGF Trap_{R1R2} formulation including “20% (wt/vol) sucrose.” Pet. 28 (citing Ex. 1016, 2798).

Although Patent Owner’s statements during prosecution of Dix establish that the Fraser formulation did, in fact, include 20% sucrose, Patent Owner contends that the “post-priority date statements cannot be relied upon to ‘fill in’ missing disclosures in the prior art as a matter of law.” Prelim. Resp. 34 (citing *Endo*, 894 F.3d at 1378–83). We find the *Endo* case to be distinguishable. In *Endo*, the claims required a benzyl benzoate co-solvent to be present in a particular ratio with the solvent and the prior art did not even disclose the use of a co-solvent in the formulation. *Endo*, 894 F.3d at 1380–1383. The court found that the prior art disclosure was insufficient to show inherency of the benzyl benzoate in the claimed ratio despite it being later revealed that it was used in the formulation because the prior art, “failed to disclose that the composition’s vehicle formulation included

another, key ingredient, benzyl benzoate, let alone the ratio of benzyl benzoate to castor oil.” *Id.* at 1383. The court also found that “there was no evidence in the record that a skilled artisan could determine the non-disclosed vehicle formulation based on the reported pharmacokinetic performance profile, or that the non-disclosed vehicle formulation was necessarily a feature of the TU injection studied in the [prior art].” *Id.* The court concluded that, “[u]nder the circumstances of this case, the incomplete description of the TU injection composition elements denied skilled artisans from having access to that composition, thereby precluding use of the inherency doctrine to fill in disclosure about the product missing from the [prior art].” *Id.*

In this case, Fraser discloses a VEGF Trap_{R1R2} formulation that includes “either 20% glycerol or 20% sucrose.” Ex. 1009, 1115. In other words, Fraser provides an option of including 20% of two different possible stabilizing agents, in contrast to the prior art in *Endo*, which did not even disclose the use of a co-solvent (and included no disclosure of any co-solvent amount). As such, we find that, on the current record, one of ordinary skill in the art would be able to “at once envisage” a VEGF Trap_{R1R2} formulation with 20% sucrose. *See Kennametal*, 780 F.3d at 1381. As a result, the Fraser disclosure does not “den[y] skilled artisans from having access to that composition,” as was the case in *Endo*.

Because we find, on the current record, that Petitioner has sufficiently shown that the VEGF Trap_{R1R2} formulation in Fraser is the same as that in Dix, we also find that Petitioner can rely on Dix to show the stability of the protein. As argued by Petitioner, Dix shows that greater than 99% of VEGF Trap_{R1R2} remained in native conformation as measured by SEC after storage for 2 months at 5° C. Ex. 1002 ¶¶ 96–102; Ex. 1021, 11:15–12:20, Table 9.

We agree with Petitioner that, while Fraser does not disclose this stability information, as evidenced by the data in Dix, such stability is necessarily a natural result of the formulation ingredients. Pet. 46 (citing *Abbott Labs. v. Baxter Pharm. Prods., Inc.*, 471 F.3d 1363, 1367 (Fed. Cir. 2006) (holding that “[o]ur cases have consistently held that a reference may anticipate even when the relevant properties of the thing disclosed were not appreciated at the time.”).

We also find that Petitioner has sufficiently shown that Fraser discloses that the VEGF Trap_{R1R2} disclosed therein was produced in CHO cells, as required by the claims. Fraser discloses that VEGF Trap_{R1R2} “was provided” by Regeneron and cites to the Holash paper in discussing the properties of VEGF Trap_{R1R2}. Ex. 1009, 1115. The Holash paper (Reference 21 in Fraser) states that “[a]ll of the VEGF-Trap variants were produced and purified from Chinese hamster ovary cells.” Ex. 1010, 11394.¹⁵

We acknowledge Patent Owner’s argument that Fraser’s citation to Holash does not mean that Fraser necessarily used CHO cells because Fraser does not “say that the VEGF Trap_{R1R2} used by the Fraser authors is the same as any of the VEGF-Trap variants described in Holash” (Prelim. Resp. 41); however, on the current record, we are persuaded by the testimony of Dr. Tarantino that the “VEGFTrap_{R1R2} disclosed in *Fraser* was created in CHO cells, and a POSA would have known as much when reading the term

¹⁵ Wulff also discloses that VEGF Trap_{R1R2} was manufactured in CHO cells and explains that the ’319 publication describes “the detailed molecular structure” of VEGF Trap_{R1R2} “and how it was created.” Ex. 1016, 2798, 2798 n.1. The ’319 publication (and the ’309 publication) also confirm that VEGF Trap_{R1R2} was produced in CHO cells. Ex. 1027 ¶ 22; Ex. 1029, Example 21; Ex. 1002 ¶¶ 93–95.

‘VEGFTrap_{R1R2}’ in the context of the whole *Fraser* article.” Ex. 1002 ¶ 93. As discussed above, Fraser refers to a particular protein, VEGF Trap_{R1R2}, and cites to a Regeneron publication (Holash) as describing the properties of this protein. Ex. 1009, 1115. Fraser then states that VEGF Trap_{R1R2} was provided by Regeneron to conduct the experiments described therein. *Id.* Based on this disclosure in Fraser, on the current record, we credit the currently unrebutted testimony of Dr. Tarantino that “[t]he reference by *Fraser* to VEGFTrap_{R1R2} being “provided” by Regeneron and directing the reader to *Holash* for a description of the protein would have informed the POSA that the VEGFTrap_{R1R2} in *Fraser* was made in CHO cells.” Ex. 1002 ¶ 94.

Patent Owner does not contest that Fraser discloses the other limitations of claims 1 and 10 and, on the current record, we find that Fraser does disclose these limitations. Accordingly, on the current record, Petitioner has demonstrated a reasonable likelihood that the subject matter of claims 1 and 10 of the ’992 patent is anticipated by the disclosure of Fraser. Petitioner also presents evidence and arguments as to how Fraser anticipates dependent claims 2–9 and 11–18. Pet. 48–53. Other than the arguments discussed above, Patent Owner does not present additional arguments further addressing the patentability of these claims. We have reviewed Petitioner’s arguments and evidence regarding these claims and find that, on the current record, Petitioner has also demonstrated a reasonable likelihood that claims 2–9 and 11–18 of the ’992 patent are anticipated by the disclosure of Fraser.

D. Asserted Obviousness over Fraser, Holash, and Wulff, in view of the '319 Publication, the '309 Publication, McNally 2000, and FDA Guidance

Petitioner contends that claims 1–18 would have been obvious over the combination of Fraser, Holash, and Wulff, in view of the '319 Publication, the '309 Publication, McNally 2000, and FDA Guidance. Pet. 53–67. Patent Owner disputes Petitioner's contentions. Prelim. Resp. 44–52.

1. Principles of Law

A claim is unpatentable under 35 U.S.C. § 103 if the differences between the subject matter sought to be patented and the prior art are such that the subject matter, as a whole, would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. *See KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007). The question of obviousness is resolved on the basis of underlying factual determinations, including: (1) the scope and content of the prior art; (2) any differences between the claimed subject matter and the prior art; (3) the level of skill in the art; and (4) when in evidence, objective evidence of non-obviousness, i.e., secondary considerations. *See Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966).

2. Petitioner's Position

Petitioner argues that it would have been obvious for one of ordinary skill in the art to produce Fraser's VEGF Trap_{R1R2} in CHO cells and formulate the resulting VEGF Trap_{R1R2} into a stable formulation for therapeutic use having the claimed stability. *See* Pet. 54–63.

First, Petitioner contends that it would have been obvious to produce Fraser's VEGF Trap_{R1R2} in CHO cells because Holash and Wulff describe

producing the same fusion protein in CHO cells. *See* Pet. 56 (citing Ex. 1016, 2798; Ex. 1010, 11393–11394). Petitioner asserts that a POSA would “stick[] to a proven method that was already shown to have worked.” *Id.* at 56–57 (citing Ex. 1002 ¶¶ 143–145, 189; Ex. 1047, 12; Ex. 1017, 1396).

Second, Petitioner contends that it would have been obvious “to select an organic cosolvent, a buffer, and a stabilizing agent as excipients for a stable formulation” because “this was the *only* formulation of aflibercept that was published for *in vivo* use.” Pet. 58 (citing Ex. 1009, 1115; Ex. 1016, 2798; Ex. 1002 ¶¶ 146–147). Petitioner asserts that Fraser teaches “this formulation sufficiently stabilized the aflibercept so that it remained useable over a two-week period when stored at 4° C.” *Id.* at 58 (citing Ex. 1009, 1115).

Third, Petitioner argues that the native conformation limitation does not distinguish the claimed formulation from the prior art. *See* Pet. 59–63. Petitioner contends that “[m]erely claiming the results achieved by an obvious combination of ingredients does not distinguish that combination from the prior art.” *Id.* at 59 (citing *In re Best*, 562 F.2d at 1255). Petitioner further argues that storage stability is not critical to the formulation and instead, “[t]his limitation appears to only be the product of simply claiming the test results reported in the examples of the ’992 patent.” *Id.* Petitioner further argues that “a POSA would have been motivated to use the *Fraser* formulation [to] make a commercial aflibercept product that was as stable as possible.” *Id.* at 60. To do so, Petitioner argues that a POSA would have been motivated to minimize aggregation, because aggregates reduce the quality and potency of the product. *See id.* (citing Ex. 1002 ¶¶ 72–74, 154). Petitioner argues that “[a] POSA thus would have regarded the preservation

of at least 98% of the aflibercept in native conformation after storage for two months at 5° C as measured by SEC as being an obvious and desirable goal, and a level of 99% or greater to be even more desirable.” *Id.* at 61 (citing Ex. 1002 ¶¶ 153).

Fourth, Petitioner argues that a POSA would have made a stable formulation—defined by the native conformation limitation—by “simply doing the obvious thing and copying the *Fraser* formulation.” Pet. 61. Petitioner argues that “[a]s of 2006, formulators possessed a relatively high degree of skill in stabilizing protein therapeutics.” *Id.* Accordingly, Petitioner argues that “a POSA would have been able to make incremental adjustments to the concentrations of polysorbate 20, phosphate buffer, aflibercept, NaCl and pH, observed their impact on stability, and then made additional adjustments as necessary until they achieved maximum stability.” *Id.* (citing Ex. 1002 ¶¶ 153–159). Petitioner argues that McNally shows that it “would have been routine and well within ordinary skill” to design and execute experiments to determine the optimal value for each variable. *See id.* at 62 (citing Ex. 1002 ¶¶ 156–159; Ex. 1013, 156–157).

3. Patent Owner’s Position

Patent Owner argues that Petitioner may not rely on inherency to demonstrate obviousness, and that Petitioner has not shown a motivation to modify the references nor a reasonable expectation of success in doing so. *See* Prelim. Resp. 45–52. First, Patent Owner argues that “Petitioner advances the same inherency argument for its obviousness ground that it did for its anticipation ground, attempting to rely on the non-prior art Dix reference.” *Id.* at 46. However, Patent Owner argues that “[t]he data from Table 9 of Dix could not have informed the POSA’s understanding of the

stability of the Fraser formulation by the critical date because it did not exist as of the critical date” *Id.*

Second, Patent Owner argues that it would not have been obvious to seek a 98% native conformation. *See* Prelim. Resp. 47–49. Patent Owner argues that “it is not the case that formulators *always* attempt to get as close to 100% native conformation as possible—only driven by hindsight would a formulator set aside other constraints and priorities and seek single-mindedly to maximize native conformation.” *Id.* at 48 (citing Ex. 1006, 2, 4, 6; Ex. 2001 ¶¶ 25–27). According to Patent Owner, Petitioner’s references “describe formulations as ‘stable’ when a much lower fraction of the product—between 90% and 95%—was present in native conformation.” *Id.* (citing Ex. 1030, 8:31–33; Ex. 1026 ¶ 63; Ex. 1024 ¶ 36; Ex. 1025 ¶ 25). Patent Owner further argues that “native conformation below 98% was consistent with certain generally applicable standards.” *Id.* at 49 (citing Ex. 2014, 14; Ex. 2021, 5).

Third, Patent Owner argues that “Petitioner has not shown that, based on information available as of the priority date, a POSA would have reasonably expected the formulation of Fraser to exhibit at least 98% native conformation under the recited conditions.” Prelim. Resp. 50. Specifically, Patent Owner argues that Fraser’s disclosure of storing the compound at 4° C for 2 weeks “does not imply that the formulation would have maintained at least 98% native conformation after two months, or anything close to it.” *Id.* at 50 (citing Ex. 1009, 1115; Pet. 58). Notably, Patent Owner argues that usability at two weeks does not imply stability over two months as aggregates tend to form over time. *See id.* (citing Ex. 2020, 4; Ex. 1021, Examples 1–3). Finally, Patent Owner argues that “adequacy of a

formulation for a preclinical study does not imply adequacy for clinical trials and approval.” *Id.* at 50–51 (citing Ex. 1013, 147; Ex. 1006, 10).

4. *Analysis*

For the reasons explained above, we find that, on the current record, Petitioner has shown that Fraser discloses the limitations of the challenged claims of the ’992 patent. However, even, *assuming arguendo*, that Fraser does not disclose certain limitations, on the current record, we find that those limitations would have been obvious based on the disclosures in the other cited references. We are persuaded by Petitioner and Dr. Tarantino’s contentions that the “prior art would have given a POSA ample motivation of making a formulation” with VEGF Trap_{R1R2} based on studies published by Regeneron showing that VEGF Trap_{R1R2} “had the best *in vivo* pharmacokinetics and anti-VEGF activity of the VEGF-trap proteins Regeneron had been studying.” Pet. 55 (citing Ex. 1009; Ex. 1010; Ex. 1016; Ex. 1029, 10 (describing VEGFTrap_{R1R2} as having “improved pharmacokinetic properties”); Ex. 1002 ¶¶ 140–142).

Petitioner has also persuasively shown that “[t]he prior art also would have motivated a POSA to select an organic cosolvent, a buffer, and a stabilizing agent as excipients for a stable formulation of aflibercept” because Regeneron’s Fraser and Wulff publications disclosed “that it had formulated aflibercept for its *in vivo* studies using the organic co-solvent polysorbate 20, a buffer containing phosphate, and the stabilizing agent sucrose.” Pet. 58 (citing Ex. 1009, 1115; Ex. 1016, 2798; Ex. 1002 ¶¶ 146–147). We are further persuaded by the contention of Petitioner and Dr. Tarantino that this was the only formulation of aflibercept that was published for *in vivo* use as of the priority date, “which would have left the

POSA with only one clear starting point when making a formulation for such use.” *Id.* (citing Ex. 1002 ¶ 147).

We are similarly persuaded by Petitioner’s contention that a POSA would have been motivated to make VEGF Trap_{R1R2} in CHO cells because Regeneron’s Wulff and Holash publications disclosed that they had done so and a POSA would have done the same in order to reproduce the desirable performance of VEGF Trap_{R1R2} in those publications. Pet. 56 (citing Ex. 1002 ¶¶ 143–145, 189; Ex. 1010, 11393–11394; Ex. 1016, 2798; Ex. 1047, 12; Ex. 1017, 1396).

Patent Owner’s main argument is that a person of ordinary skill in the art would not have been motivated to produce a VEGF Trap_{R1R2} formulation in which 98% of the VEGF antagonist is present in native conformation following storage at 5° C for two months, nor would a POSA have had a reasonable expectation of success in doing so. Patent Owner also argues that Petitioner may not use Dix to demonstrate obviousness of the claimed stability requirements because they allege that Petitioner cannot rely on inherency in the context of its obviousness arguments. Prelim. Resp. 44–52. Patent Owner contends that *In re Best* is distinguishable because “Petitioner’s inherency argument is mistaken in the context of its anticipation argument, and Petitioner does not make a parallel single-reference obviousness argument [as in *Best*].” *Id.* at 47 n.1. Patent Owner also contends that “no party in *Best* attempted to show inherency with non-prior art data.” *Id.*

As explained above, based on the current record, we do not find Petitioner’s inherency arguments in the context of its anticipation argument to be “mistaken.” Also, while we invite the parties to further brief this issue, we are not persuaded that the reasoning in *In re Best* is limited to the context

of a single-reference obviousness argument as asserted by Patent Owner. We are similarly unpersuaded that *In re Best* does not apply to situations in which inherency is shown with non-prior art data.

On the current record, we find that Petitioner has persuasively shown that a person of ordinary skill in the art would have been able to achieve the claimed stability limitations by making the VEGF Trap_{R1R2} formulation disclosed in Fraser and Wulff. On the current record, we also agree with Petitioner that, if needed, one of skill in the art would have been able to optimize the Fraser formulation in view of the other cited references in order to achieve the claimed stability. *See E.I. DuPont de Nemours v. Synvina C.V.*, 904 F.3d 996, 1006 (Fed. Cir. 2018) (The fact that routine or trial-and-error experiments may be required to determine the optimum concentrations of ingredients in an otherwise old or obvious formulation does not make the optimized formulation inventive).

Thus, after carefully considering the arguments and evidence, we determine that, on this record, Petitioner has demonstrated a reasonable likelihood that the subject matter of claims 1 and 10 of the '992 patent would have been obvious over the disclosures of Fraser, Holash, and Wulff, in view of the '319 Publication, the '309 Publication, McNally 2000, and FDA Guidance. Petitioner also presents evidence and arguments as to how these references render obvious dependent claims 2–9 and 11–18 of the '992 patent. Pet. 63–66. Other than the arguments discussed above, Patent Owner does not present additional arguments further addressing the patentability of these claims. We have reviewed Petitioner's arguments and evidence regarding these claims and find that, on the current record, Petitioner has demonstrated a reasonable likelihood that the subject matter of claims 2–9 and 11–18 of the '992 patent is rendered obvious by the

disclosure of Fraser, Holash, and Wulff, in view of the '319 Publication, the '309 Publication, McNally 2000, and FDA Guidance.

V. CONCLUSION

For the forgoing reasons, Petitioner has demonstrated a reasonable likelihood that at least one challenged claim of the '992 patent is anticipated by and/or would have been obvious over the prior art of record.

Accordingly, we institute an *inter partes* review on claims 1–18 for all grounds set forth in the Petition.

VI. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that, pursuant to 35 U.S.C. § 314, an *inter partes* review is instituted on claims 1–18 for all grounds set forth in the Petition; and

FURTHER ORDERED that, pursuant to 35 U.S.C. § 314(c) and 37 C.F.R. § 42.4, *inter partes* review of the '992 patent shall commence on the entry date of this Order, and notice is hereby given of the institution of a trial.

IPR2023-00462
Patent 10,464,992 B2

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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

CELLTRION, INC.,
Petitioner,

v.

REGENERON PHARMACEUTICALS, INC.,
Patent Owner.

IPR2023-00462
Patent 10,464,992 B2

Before JOHN G. NEW, SUSAN L. C. MITCHELL, and JAMIE T. WISZ,
Administrative Patent Judges.

WISZ, *Administrative Patent Judge.*

DECISION
Granting Institution of *Inter Partes* Review
35 U.S.C. § 314

I. INTRODUCTION

Celltrion, Inc. (“Petitioner”) filed a Petition (Paper 2, “Pet.”) requesting an *inter partes* review of claims 1–18 of U.S. Patent No. 10,464,992 (Ex. 1001, “the ’992 patent”). Regeneron Pharmaceuticals, Inc. (“Patent Owner”) filed a Preliminary Response (Paper 6, “Prelim. Resp.”). With Board authorization, Petitioner filed a Pre-Institution Reply (Paper 9, “Reply”), and Patent Owner filed a Sur-Reply (Paper 10, “Sur-Reply”).

Under 35 U.S.C. § 314(a), the Board “may not authorize an *inter partes* review to be instituted unless . . . the information presented in the petition . . . and any response . . . shows that there is a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition.” After considering the Petition, the Preliminary Response, the Reply, the Sur-reply, and the evidence of record, we determine that Petitioner has demonstrated a reasonable likelihood of prevailing with respect to at least one claim challenged in the Petition. Accordingly, we institute an *inter partes* review of claims 1–18 of the ’992 patent, based on all of the grounds identified in the Petition. *See SAS Inst. Inc. v. Iancu*, 138 S. Ct. 1348, 1354, 1359–60 (2018); 37 C.F.R. § 42.108(a) (“When instituting post-grant review, the Board will authorize the review to proceed on all of the challenged claims and on all grounds of unpatentability asserted for each claim.”).

The following findings of fact and conclusions of law are not final, but are made for the sole purpose of determining whether Petitioner meets the threshold for initiating review. Any final decision shall be based on the full trial record, including any response timely filed by Patent Owner. Any arguments not raised by Patent Owner in a timely-filed Response may be deemed waived, even if they were presented in the Preliminary Response.

II. BACKGROUND

A. *Real Parties-in-Interest*

Petitioner identifies Celltrion, Inc., Celltrion Healthcare Co. Ltd. and Celltrion Healthcare U.S.A., Inc. as the real parties-in-interest. Pet. 39. Patent Owner identifies Regeneron Pharmaceuticals, Inc. as the real party-in-interest. Paper 4, 1.

B. *Related Matters*

The parties identify the following district court litigation involving the '992 patent: *Regeneron Pharmaceuticals, Inc. v. Mylan Pharmaceuticals Inc.*, Case No. 1-22-cv-00061 (N.D.W.V), filed on August 2, 2022. Pet. 39; Paper 4, 1.

The parties identify two matters related to the '992 patent filed at the USPTO: (1) *ex parte* reexamination Control No. 90/014,448 (pending); (2) *Chengdu Kanghong Biotechnology Co., Ltd. v. Regeneron Pharms., Inc.*, IPR2021-00402 (PTAB Jan. 7, 2021) (terminated). Pet. 39; Paper 4, 1.

Patent Owner identifies other *inter partes* review proceedings challenging related patents. See Paper 4, 1–3. The pending proceedings (excluding joined cases) include:

Mylan Pharms. Inc. v. Regeneron Pharms., Inc., IPR2021-00880, challenging claims of U.S. Patent No. 9,669,069 B2, Final Written Decision (Paper 89) issued Nov. 9, 2022;

Mylan Pharms. Inc. v. Regeneron Pharms. Inc., IPR2021-00881, challenging claims of U.S. Patent No. 9,254,338 B2, Final Written Decision (Paper 94) issued Nov. 9, 2022;

Mylan Pharms. Inc. v. Regeneron Pharms., Inc., IPR2022-01225, challenging claims of U.S. Patent No. 10,130,681 B2, Institution Decision (Paper 21) issued Jan. 11, 2023;

Samsung Bioepis Co. Ltd. v. Regeneron Pharms., Inc., IPR2023-00442, challenging claims of U.S. Patent No. 10,130,681 B2, petition filed Jan. 6, 2023;

Mylan Pharms. Inc. v. Regeneron Pharms., Inc., IPR2023-00099, challenging claims of U.S. Patent No. 10,857,205 B2, Decision Denying Institution (Paper 10) due to statutory disclaimer issued Mar. 1, 2023;

Mylan Pharms. Inc. v. Regeneron Pharms., Inc., IPR2022-01226, challenging claims of U.S. Patent No. 10,888,601 B2, Institution Decision (Paper 22) issued Jan. 11, 2023; and

Apotex, Inc. v. Regeneron Pharms., Inc., IPR2022-01524, challenging claims of U.S. Patent No. 11,253,572 B2, Decision Denying Institution (Paper 9) issued Mar. 10, 2023. *Id.*

Finally, Patent Owner lists the following pending applications as related to the '992 patent: U.S. Patent Application Nos. 17/072,417, 17/112,404, 17/112,063, and 17/350,958. *Id.*

C. The '992 Patent

The '992 patent is titled “VEGF Antagonist Formulations Suitable for Intravitreal Administration.” Ex. 1001, code (54). The '992 patent is directed to pharmaceutical formulations containing a vascular endothelial growth factor (“VEGF”) antagonist. *Id.* at 1:30–34. The '992 patent defines the term “VEGF antagonist” as a “compound capable of blocking or inhibiting the biological action of [VEGF], and includes fusion proteins capable of trapping VEGF.” *Id.* at 6:9–12. The '992 patent refers to such a fusion protein as a “VEGF trap” and discloses that it comprises “an

immunoglobulin-like (Ig) domain 2 of a first VEGF receptor and Ig domain 3 of a second VEGF receptor, and a multimerizing component.” *Id.* at 2:7–11. “In specific embodiments, the VEGF antagonist is expressed in a mammalian cell line such as a [Chinese Hamster Ovary (“CHO”)] cell and may be modified post-translationally.” *Id.* at 6:14–16.

According to the ’992 patent, “[p]roteins possess unique chemical and physical properties that present stability problems: a variety of degradation pathways exist for proteins, implicating both chemical and physical instability.” Ex. 1001, 5:37–40. In one embodiment, the ’992 patent describes “a stable pharmaceutically acceptable formulation comprising a VEGF antagonist.” *Id.* at 6:41–54. “The formulation can also comprise one or more pharmaceutically acceptable carriers, buffers, tonicity agents, stabilizers, and/or excipients.” *Id.* at 6:47–49. “An example of a pharmaceutically acceptable liquid formulation comprises a VEGF antagonist . . . , a buffer, an organic co-solvent such as polysorbate, a tonicity agent such as NaCl, and optionally, a stabilizer such as sucrose or trehalose.” *Id.* at 6:49–54.

The ’992 patent provides eight examples of VEGF Trap formulations and their corresponding stability test data. *See* Ex. 1001, 8:8–12:30. Examples 1–4 describe liquid formulations include varying amounts of VEGF Trap (SEQ ID NO: 4), phosphate, NaCl, polysorbate 20 or polyethylene glycol, and sucrose. *See id.* at 8:8–9:55. Examples 1–4 further disclose that the formulations contain at least 98% of VEGF Trap present in native configuration following storage at 5° C for two months as measured by size exclusion chromatography (“SEC”). *See id.*

D. Challenged Claims

Petitioner challenges claims 1–18 of the '992 patent. Pet. 1. Claims 1 and 10, which are the independent claims of the '992 patent, are illustrative of the challenged claims and are reproduced below, with the only difference being claim 1 describes a vial comprising a formulation and claim 10 describes the formulation.

1. A vial comprising:

a vascular endothelial growth factor (VEGF) antagonist,

an organic co-solvent,

a buffer, and

a stabilizing agent,

wherein the VEGF antagonist is a fusion protein produced in a Chinese Hamster Ovary (CHO) cell, the fusion protein comprising an immunoglobulin-like (Ig) domain 2 of a first VEGF receptor and Ig domain 3 of a second VEGF receptor, and a multimerizing component; and

wherein at least 98% of the VEGF antagonist is present in native conformation following storage at 5° C. for two months as measured by size exclusion chromatography.

Ex. 1001, 19:31–43.

10. A formulation comprising:

a vascular endothelial growth factor (VEGF) antagonist,

an organic co-solvent,

a buffer, and

a stabilizing agent,

wherein the VEGF antagonist is a fusion protein produced in a Chinese Hamster Ovary (CHO) cell, the fusion protein comprising an immunoglobulin-like (Ig) domain 2 of a first VEGF receptor and Ig domain 3 of a second VEGF receptor, and a multimerizing component; and

wherein at least 98% of the VEGF antagonist is present in native conformation following storage at 5° C. for two months as measured by size exclusion chromatography.

Id. at 19:65–20:40. Claims 2–9 and 11–18 depend from claims 1 and 10, either directly or indirectly.

E. The Asserted Grounds of Unpatentability

Petitioner asserts that claims 1–18 would have been unpatentable on the following grounds:

Ground	Claim(s) Challenged	35 U.S.C. § ¹	Reference(s)/Basis
1	1–18	102	Fraser ²
2	1–18	103	Fraser, Wulff ³ , Holash ⁴ , '319 Publication ⁵ , '309 Publication ⁶ , McNally

¹ The Leahy-Smith America Invents Act (“AIA”), Pub. L. No. 112–29, 125 Stat. 284 (2011), amended 35 U.S.C. § 103, was effective on March 16, 2013. Because the '992 patent claims priority to a provisional application that has a filing date before March 16, 2013, and Petitioner does not currently contest this priority date, we apply the pre-AIA version of § 103. We note that our analysis in this Decision would not change under AIA law.

² Fraser, Hamish M. et al., *Single Injections of Vascular Endothelial Growth Factor Trap Block Ovulation in the Macaque and Produce a Prolonged, Dose-Related Suppression of Ovarian Function*, J. Clin. Endocrinology & Metabolism, Vol. 90, No. 2, 1114–1122 (2005) (Ex. 1009, “Fraser”).

³ Wulff, Christine et al., *Prevention of Thecal Angiogenesis, Antral Follicular Growth, and Ovulation in the Primate by Treatment with Vascular Endothelial Growth Factor Trap R1R2*, Endocrinology, Vol. 143, No. 7, 2797–2807 (2002) (Ex. 1016, “Wulff”).

⁴ Holash, Jocelyn et al., *VEGF-Trap: A VEGF blocker with potent antitumor effects*, PNAS, Vol. 99, No. 17, 11393–11398 (2002) (Ex. 1010, “Holash”).

⁵ Papadopoulos et al., WO 00/75319 A1, published Dec. 14, 2000 (Ex. 1029, “the '319 publication”).

⁶ Kandel et al., US 2004/0265309 A1, published Dec. 30, 2004 (Ex. 1027, “the '309 publication”).

Ground	Claim(s) Challenged	35 U.S.C. § ¹	Reference(s)/Basis
			2000 ⁷ , FDA Guidance ⁸

Pet. 41. Petitioner submits the Declaration of Ralph Tarantino, R.Ph., Ph.D. (Ex. 1002) in support of institution of *inter partes* review. Patent Owner submits the Declarations of Alexander M. Klibanov, Ph.D. (Ex. 2001) and David M. Brown, M.D. (Ex. 2004).

F. Asserted Prior Art

1. Fraser (Ex. 1009)

Fraser, titled “Single Injections of Vascular Endothelial Growth Factor Trap Block Ovulation in the Macaque and Produce a Prolonged, Dose-Related Suppression of Ovarian Function,” describes a study that evaluated “a potent, receptor-based VEGF antagonist, the VEGF trap.” Ex. 1009, 1114. Specifically, Fraser describes administering VEGF Trap_{R1R2}, “a recombinant, chimeric protein comprising Ig domain 2 of human VEGF-R1 and Ig domain 3 of human VEGF-R2, expressed in sequence with the human [fragment crystallizable (Fc) region].” *Id.* at 1115. According to Fraser, “[c]ompared with earlier versions of receptor-based fusion proteins, the VEGF Trap_{R1R2} exhibits greater affinity for VEGF-A (affinity constant—1 pM) as well as improved bioavailability and pharmacokinetic properties.” *Id.* (citing Holash, Ex. 1010).

⁷ Paul McGoff & David S. Scher, *Solution Formulation of Proteins/Peptides* in PROTEIN FORMULATION AND DELIVERY vol. 99, 139–58 (Eugene J. McNally ed., 2000) (Ex. 1013, “McNally 2000”).

⁸ Food & Drug Administration, *Guidance for Industry, Container Closure Systems for Packaging Human Drugs and Biologics* (May 1999) (Ex. 1038, “FDA Guidance”).

Fraser further describes a formulation in which “VEGF Trap_{R1R2} (Regeneron Pharmaceuticals, Inc., Tarrytown, NY) was provided at a concentration of 24.3 mg/ml in 2-ml aliquots in buffer composed of 5 mM phosphate, 5 mM citrate, 100 mM NaCl (pH 6.0), and 0.1% wt/vol Tween 20, with either 20% glycerol or 20% sucrose.” Ex. 1009, 1115. “The compounds were stored at -20 C until required, at which time they were thawed. Any compound remaining was stored at 4 C and used within 2 wk.” *Id.*

2. *Dix (Ex. 1021)*⁹

Dix, titled “VEGF Antagonist Formulations,” describes a stable liquid formulation including a VEGF-specific fusion protein antagonist. Ex. 1021, codes (54), (57). Dix refers to the antagonist as a “VEGF ‘trap’” that comprises “a receptor component consisting essentially of an immunoglobulin-like (Ig) domain 2 of a first VEGF receptor and Ig domain 3 of a second VEGF receptor, and a multimerizing component.” *Id.* at 1:43–54. Dix provides several examples of formulations including VEGF trap (SEQ ID NO: 4). *See id.* at 7:7–12:20. In one embodiment, the formulation contains “about 5 mM phosphate, 5 mM citrate, 100 mM NaCl, 0.1% polysorbate 20, 20% sucrose, and 25 mg/ml VEGF trap protein.” *Id.* at 11:15–20. The formulation is characterized by a pH ranging from 6.0–6.1. *Id.* Stability testing over 36 months at 5° C provided the following results:

⁹ Dix et al., US 8,110,546 B2, issued Feb. 7, 2012 (Ex. 1021, “Dix”). Petitioner relies on Dix as evidence “that the claimed level of stability is the natural result of the ingredients in the *Fraser* formulation.” *See* Pet. 47.

TABLE 9

Stability and Activity of Liquid Formulation (VEGF-FS405)				
Months	% Native Configuration	Bioassay	Binding Assay	Protein Content mg/ml
0	99.7	106	72	25.0
1	99.9	119	4.4 pM*	25.2
2	99.6	102	5.4 pM*	25.1
3	99.6	97	88	25.1
6	99.6	101	106	25.0
9	99.4	89	136	25.4
12	99.5	85	95	25.2
18	99.4	99	81	25.5
24	99.3	75	95	25.6
36	98.8	109	79	25.6

Id. at 12:5–20.

3. *Wulff (Ex. 1016)*

Wulff, titled “Prevention of Thecal Angiogenesis, Antral Follicular Growth, and Ovulation in the Primate by Treatment with Vascular Endothelial Growth Factor Trap R1R2,” describes a study that evaluated the anti-angiogenic properties of VEGF Trap R1R2. Ex. 1016, 2797. Wulff describes “VEGF Trap R1R2 used in these experiments [as] a recombinant chimeric protein comprising portions of the extracellular, ligand binding domains of the human VEGF receptors Flt-1 (VEGF-R1, Ig domain 2) and KDR (VEGF-R2, Ig domain 3) expressed in sequence with the Fc portion of human [immunoglobulin G (IgG)].” *Id.* at 2798, Fig. 1.

Figure 1 is reproduced below:

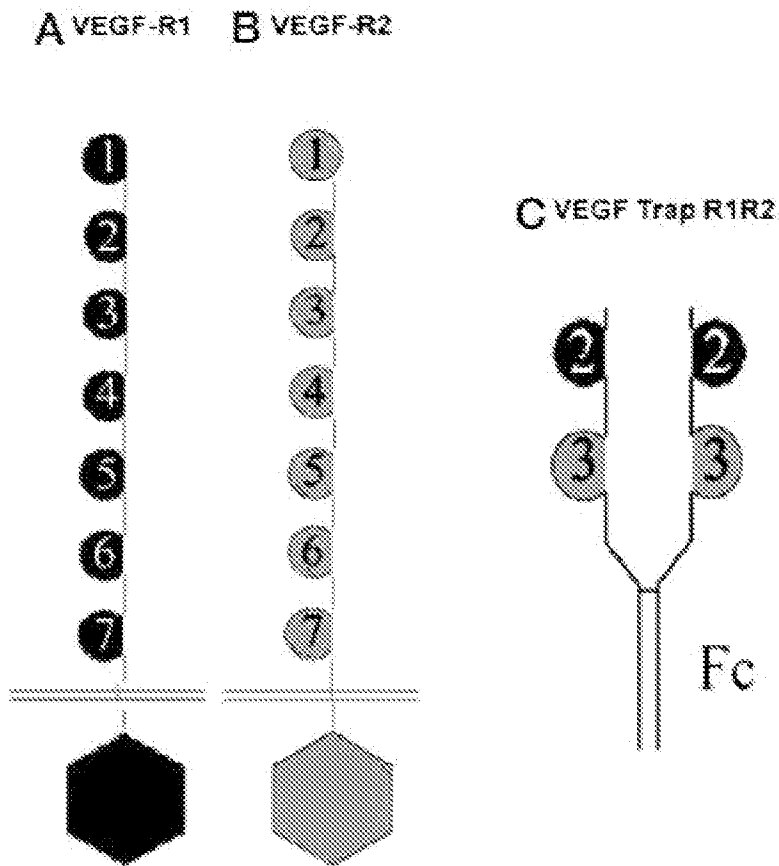


Figure 1A and 1B illustrates VEGF receptors R1 and R2, respectively. Ex. 1016, 2798. VEGF-R1 and VEGF-R2 are each illustrated as a line extending from an intracellular domain (filled hexagon), across a cell membrane (double-line), to seven extracellular domains individually illustrated as numbered circles on the line. *See id.* “These extracellular domains are responsible for VEGF binding.” *Id.* Figure 1C illustrates VEGF Trap R1R2 as including the Fc portion of IgG with two extending arms, each including domain 2 of VEGF-R1 and domain 3 of VEGF-R2 shown as circles numbered 2 and 3, respectively. *See id.*

Wulff discloses that “[t]he presence of the Fc domain results in homodimerization of the recombinant protein, thereby creating a high affinity (KD1-5pM) VEGF Trap.” Ex. 1016, 2798. Wulff further discloses that “the detailed molecular structure” of the VEGF Trap is described in the

PCT Publication WO 00/75319 A1 (the '319 application) (Ex. 1029). *Id.* at 2798 n.1. Additionally, according to Wulff, “[t]he VEGF trap was expressed in CHO cells and was purified by protein A affinity chromatography followed by size-exclusion chromatography.” *Id.* at 2798.

4. *Holash (Ex. 1010)*

Holash is titled “VEGF-Trap: A VEGF blocker with potent antitumor effects.” Ex. 1010, 11393. Holash describes engineering VEGF Traps. *Id.* Specifically, Holash describes the following process:

The parental VEGF-Trap was created by fusing the first three Ig domains of VEGFR₁ to the constant region (Fc) of human IgG1. VEGF-Trap_{ΔB1} was created by removing a highly basic 10-aa stretch from the third Ig domain of the parental VEGF-Trap. VEGF-Trap_{ΔB2}, was created by removing the entire first Ig domain from VEGF-Trap_{ΔB1}. VEGF-Trap_{R1R2} was created by fusing the second Ig domain of VEGFR1 with the third Ig domain of VEGFR2. All of these VEGF-Trap variants were produced and purified from Chinese hamster ovary cells.

Id. at 11393–11394.

5. *The '309 publication (Ex. 1027)*

The '309 publication, titled “Method of Tumor Regression with VEGF Inhibitors,” relates to methods of administering a VEGF blocker to reduce tumor size and inhibit tumor metastases. Ex. 1027, codes (54), (57). The '309 publication states that, in a “preferred embodiment, the VEGF trap is VEGFR1R2-FcΔC1(a) (also termed VEGF trap_{R1R2}) having the nucleotide sequence set forth in SEQ ID NO: 1 and the amino acid sequence set forth in SEQ ID NO: 2.” *Id.* ¶¶ 5, 22. It also states, “[f]or a complete description of VEGF-receptor based antagonists including VEGFR1R2- FcΔC1(a), see PCT publication WO/00/75319, the contents of which is herein incorporated by reference in its entirety.” *Id.* ¶ 22.

6. *The '319 publication (Ex. 1029)*

The '319 publication, titled “Modified Chimeric Polypeptides with Improved Pharmacokinetic Properties,” relates to VEGF antagonists. Ex. 1029, code (54), 10:3–14. More specifically, the '319 publication describes VEGF antagonists including a VEGF receptor component linked to a multimerizing component. *Id.* at 10:3–14. The VEGF receptor component includes Ig domain 2 of the extracellular domain of a first VEGF receptor and Ig domain 3 of the extracellular domain of a second VEGF receptor. *Id.* The '319 publication further describes a host-vector system for producing the fusion polypeptide, wherein a CHO cell is the host cell. *Id.* at 12:19–26.

7. *McNally 2000 (Ex. 1013)*

McNally 2000 is titled “Solution Formulation of Proteins/Peptides.” Ex. 1013, 139. McNally 2000 explains that “[t]he simplest and most economical way to formulate a protein is to develop a solution formulation.” *Id.* According to McNally, a formulation scientist can determine whether a solution formulation will be acceptable for a given protein. *Id.* The scientist can use initial formulation studies to identify problems such as poor solubility or aggregation. *See id.* “For example, a particular pH or mix of buffer components used during processing may reduce solubility or induce aggregation.” *Id.* at 139–140.

McNally 2000 further describes analytical test procedures for characterizing the physicochemical properties of the protein. Ex. 1013, 140. Typical properties monitored include conformation and size using size exclusion chromatography (SEC). *Id.*

McNally provides a “step-by-step[] how-to protocol” for a protein solution formulation development study. Ex. 1013, 156–157. “Ideally, the

protein concentration and solubility are determined first to establish a working range for the initial pH stability study.” *Id.* at 156. “The next phase of experiments should focus on a narrower pH and concentration range and should study higher temperatures, possibly adding stabilizing excipients and extending the time frame of the study to at least one year. *Id.* at 157. “Specific buffer ion effects could be investigated during this phase.” *Id.*

8. *FDA Guidance (Ex. 1038)*

FDA Guidance is titled “Guidance for Industry, Container Closure Systems for Packaging Human Drugs and Biologics.” Ex. 1038. The Guidance provides general principles for submitting information on packaging materials used for human drugs and biologics. *Id.* at 1. The FDA Guidance explains that “[i]njectable dosage forms represent one of the highest risk drug products” because “[a]ny contaminants present . . . can be rapidly and completely introduced into the patient’s general circulation. *Id.* at 23–24. Injectable products, whether small-volume or large-volume parenterals, may be packaged in vials. *Id.*

III. DENIAL UNDER 35 U.S.C. § 325(d)

Patent Owner asserts that we should deny the Petition under 35 U.S.C. § 325(d) because the Petition presents substantially the same art and arguments that the Office previously analyzed and fails to show that the Office erred during prosecution. *See* Prelim. Resp. 58–68.

We have discretion to deny review when “the same or substantially the same prior art or arguments previously were presented to the Office.” 35 U.S.C. § 325(d) (“Section 325(d)”). In that respect, Section 325(d) provides that the Director may elect not to institute a proceeding if the challenge to the patent is based on matters previously presented to the

Office.¹⁰ *Advanced Bionics, LLC v. Med-El Elektromedizinische Geräte GmbH*, IPR2019-01469, Paper 6 at 7 (PTAB Feb. 13, 2020) (precedential) (“*Advanced Bionics*”).

In evaluating the exercise of discretion to deny institution under Section 325(d), the Board uses the following two-part framework: (1) determining whether the same or substantially the same art previously was presented to the Office or whether the same or substantially the same arguments previously were presented to the Office; and (2) if either condition of the first part of the framework is satisfied, determining whether the petitioner has demonstrated that the Office erred in a manner material to the patentability of challenged claims. *Advanced Bionics*, Paper 6 at 8.

In applying the two-part framework, we consider several non-exclusive factors, including:

- (a) the similarities and material differences between the asserted art and the prior art involved during examination;
- (b) the cumulative nature of the asserted art and the prior art evaluated during examination;
- (c) the extent to which the asserted art was evaluated during examination, including whether the prior art was the basis for rejection;
- (d) the extent of the overlap between the arguments made during examination and the manner in which petitioner relies on the prior art or patent owner distinguishes the prior art;
- (e) whether petitioner has pointed out sufficiently how the examiner erred in its evaluation of the asserted prior art; and
- (f) the extent to which additional evidence and facts presented in the petition warrant reconsideration of the prior art or arguments.

¹⁰ The Board institutes trial on behalf of the Director. 37 C.F.R. § 42.4(a).

Becton, Dickinson & Co. v. B. Braun Melsungen AG, IPR2017-01586, Paper 8 at 17–18 (PTAB Dec. 15, 2017) (precedential as to Section III.C.5, first paragraph) (“*Becton, Dickinson*”).

Factors (a), (b), and (d) relate to whether the art or arguments presented in the Petition are the same or substantially the same as those previously presented to the Office. *Advanced Bionics*, Paper 6 at 10. Factors (c), (e), and (f) “relate to whether the petitioner has demonstrated a material error by the Office” in its prior consideration of that art or arguments. *Id.* Only if the same or substantially the same art or arguments were previously presented to the Office do we then consider whether petitioner has demonstrated a material error by the Office. *Id.*

A. The ’992 Patent Prosecution History

The original application for the ’992 patent was filed with a preliminary amendment cancelling claims 1–11 and listing new claims 12–29. Ex. 1004, 2–4.¹¹ Claims 12 and 21 were identical to now-issued claims 1 and 10, except that they lacked the last clause of the claims reciting the presence of at least 98% of the VEGF antagonist in native conformation following storage. *See id.*

In a Non-Final Action dated April 2, 2019, the Examiner rejected claims 12–29 for nonstatutory double patenting. Ex. 1004, 74–79. Specifically, the Examiner rejected claims 12–29 as being unpatentable over claims 1–7 and 11–17 of U.S. Patent No. 8,092,803 (“the ’803 patent”), claims of other related patents, and claims 12–26 of co-pending Application No. 15/879,294. *See id.* at 77–79.

¹¹ The cited page numbers in Exhibit 1004 refer to the page numbers added by Petitioner in the bottom-right corner of the page.

In response, the applicant amended pending claims 12 and 21 to recite the native conformation limitation recited by now-issued claims 1 and 10, respectively. Ex. 1004, 90–91. The applicant filed a terminal disclaimer as to the '803 patent. *See id.* at 93, 96. The applicant argued that the amended claims were patentably distinct from the other patents and application asserted in the double-patenting rejection. *See id.* at 93–94. Specifically, the applicant argued that “[i]ndependent claims 12 and 21 have been amended to include an element relating to the stability of the protein conformation in storage over a period of time. This element is not contained within any of the claims” asserted by the Examiner in the double-patenting rejection, excluding the '803 patent. *Id.* Following the amendment and terminal disclaimer, the Examiner allowed the claims. *Id.* at 104–111.

B. Same or Substantially the Same Art or Arguments Previously Presented to the Office

We first consider whether Petitioner asserts the same or substantially the same art or arguments that previously were presented to the Office. *Advanced Bionics*, Paper 6 at 8. Patent Owner contends that “Petitioner’s primary reference for both Grounds 1 and 2, Fraser (Ex.1009), was cited in an [Information Disclosure Statement (‘IDS’)] during prosecution of the application that resulted in the '992 patent. The Examiner signed the IDS as considered and thus is presumed to have considered it.” Prelim. Resp. 53 (citing *Husky Injection Molding Systems, Ltd., et al., v. Plastipak Packaging, Inc.*, IPR2020-00428, Paper 24 at 11 (PTAB July 28, 2020)). Patent Owner also contends that Holash was presented to the Patent Office because “Holash (Ex.1010) is expressly cited in the specification of the '992 patent and incorporated by reference in its entirety.” *Id.* at 54 (citing Ex. 1001, 1:50–52).

Patent Owner further argues that we should find Petitioner's additional references to be substantially the same as art that was presented to the Office. *See* Prelim. Resp. 54–60. First, Patent Owner contends that WO 2006/104852 (Ex. 2022) and U.S. Patent Publication No. 2006/0217311 (Ex. 2023), which were provided to the Examiner during prosecution, include the same data as in the Dix patent on which Petitioner relies. *Id.* at 54–56 (citing Ex. 1001, code (56); Ex. 1004, 87; Ex. 2022; Ex. 2023). Patent Owner also contends that Wulff is cumulative to Fraser (disclosing “the effects of a VEGF antagonist on the reproductive system of primates”) and Holash (disclosing “using CHO cells to produce the VEGF antagonist”). *See id.* at 56–57.

Additionally, Patent Owner contends that “both Wulff (Ex.1016) and the '319 Publication (Ex.1029) were considered during prosecution of a continuation application filed by Patent Owner, Ex.2024; Ex.2025, which issued as U.S. Patent No. 11,066,458 [“the '458 patent”], Ex.2026.” Prelim. Resp. 57. Patent Owner further contends that the relevant disclosures of the '309 Publication are cumulative of the '319 Publication, which was before the Patent Office during the prosecution of the '458 patent. *Id.* at 58.

Finally, Patent Owner contends that McNally 2000 and FDA Guidance “both simply describe general knowledge of the POSA.” Prelim. Resp. 59. “Patent Owner does not dispute that these two references would have been part of the general knowledge of a POSA.” *Id.*

Petitioner asserts that the “petition presents art and arguments that are materially different than those presented to the Office during prosecution of the '992 patent” and that the only rejections made during prosecution of the

application that led to the '992 patent were obviousness-type double-patenting rejections. Pet. 33.

Petitioner further argues that the prosecution of the prior applications in the patent family indicates that the Examiner did not consider the cited references. *See* Pet. 33–34. Specifically, Petitioner asserts that “[t]he prosecution histories of these applications do not contain any rejections over the prior art. Rather, the claims in the priority application were rejected only for obviousness-type double patenting, written description, and indefiniteness.” *Id.* (citing Exs. 1039–1046). Petitioner contends that “reviewing the prosecution of all of the priority applications, in which no rejections over the prior art were made, but rather the claims were rejected for obviousness-type double patenting, it is apparent that the Examiner did not consider the *Fraser* reference.” *Id.* at 34.

Finally, Petitioner argues that the Petition “raises new arguments about *Fraser* not before the Office during prosecution that are based on new evidence and prior art that were not before the Office during prosecution.” Pet. 35. For example, Petitioner argues that “the '319 *Publication* or the '309 *Publication*, [disclose] that the VEGF Trap_{R1R2} protein in the *Fraser* formulation is aflibercept.” *Id.* Petitioner argues that Wulff discloses “that Regeneron’s VEGF Trap_{R1R2} protein was made using CHO cells.” *Id.* And Petitioner argues that Dix discloses that “Patent Owner’s own tests established that the *Fraser* formulation met (and indeed exceeded) the 99% native conformation limitation of the challenged claims.” *Id.*

We agree with Patent Owner that *Fraser* was cited during prosecution of the application that led to the '992 patent and was, therefore, previously presented to the Office. *Advanced Bionics*, Paper 6 at 7–8 (“Previously presented art includes art made of record by the Examiner, and art provided

to the Office by an applicant, such as on an [IDS], in the prosecution history of the challenged patent.”); Ex. 1004, 87. Because Fraser is Petitioner’s sole reference for Ground 1, and primary reference for Ground 2, we, therefore, find that the same or substantially the same art was previously presented regardless of whether the other references are cumulative of ones that were presented during prosecution.

C. Whether the Office Erred in a Manner Material to Patentability

Because we find that the same or substantially the same art previously was presented to the Office, we turn to whether Petitioner demonstrates that the Office erred in a manner material to the patentability of the challenged claims. *Advanced Bionics*, Paper 6 at 8, 10; *see Becton, Dickinson*, Paper 8 at 24.

Petitioner contends that “through no fault of the examiner, the Office erred to any extent it evaluated *Fraser*.” Pet. 36. Petitioner also argues that the petition “raises new arguments about *Fraser* not before the Office during prosecution that are based on new evidence” and explains how the Examiner erred in failing to apply Fraser against the claims. *Id.* at 35–36.

Patent Owner contends that Petitioner has not established error with respect to Fraser and that “Petitioner does not allege material error by the Patent Office with respect to any of [the] other key prior art, and there is none.” Prelim. Resp. 62.

We find that Petitioner has sufficiently shown error in this case. As discussed further below with respect to the Grounds, the Petition establishes that the VEGF Trap_{R1R2}¹² protein disclosed in Fraser is the same as the one

¹² The term “VEGF Trap_{R1R2}” is denoted as “VEGF Trap_{R1R2},” “VEGFTrap_{R1R2}” and “VEGF trap_{R1R2}” in the briefing and references. Petitioner also uses the term “aflibercept” interchangeably with these terms.

disclosed in the Dix publication. Petitioner has also shown that Fraser's VEGF Trap_{R1R2} formulation is the same as that disclosed in Dix, which establishes that the Fraser formulation meets the 98% native conformation limitation of the challenged claims. We, therefore, find that the Petitioner demonstrates that the Examiner misapprehended or overlooked the teachings of Fraser in this regard, and we decline to exercise our discretion to deny institution under 35 U.S.C. § 325(d).

IV. ANALYSIS

A. *Person of Ordinary Skill in the Art*

“The level of skill in the art is a factual determination” that provides a primary guarantee of objectivity in an obviousness analysis. *Al-Site Corp. v. VSI Int'l Inc.*, 174 F.3d 1308, 1324 (Fed. Cir. 1999) (citing *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966); *Ryko Mfg. Co. v. Nu-Star, Inc.*, 950 F.2d 714, 718 (Fed. Cir. 1991)).

Petitioner asserts that a person of ordinary skill in the art (“POSA”) at the time of the invention “would have had a Ph.D. in pharmaceutical sciences or a similar field, with at least several years of experience in the development, manufacture and characterization of formulations of therapeutic proteins, including, for example, fusion proteins or antibodies.” Pet. 30 (citing Ex. 1002 ¶¶ 39–43). Petitioner further asserts that the POSA “would have understood how to combine proteins with compatible excipients such as surfactants, stabilizers, salts and buffers of various pH values, and how to adjust these combinations in order to optimize their stability in liquid or solid form.” *Id.* at 30–31. Petitioner asserts that the

Because Fraser uses the term “VEGF Trap_{R1R2}” (Ex. 1009, 1115), we use the same nomenclature in this Decision.

POSA would have been able to assess stability and compatibility by using “state-of-the-art analytical methods, such as SEC.” *Id.* at 31.

Patent Owner does not contest the characterization offered by Petitioner. *See* Prelim. Resp. 16.

For purposes of this Decision, we adopt Petitioner’s characterization because it is consistent with the level of skill in the art at the time of the invention as reflected by the ’992 patent and the cited prior art. *See Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001) (explaining that specific findings regarding ordinary skill level are not required “where the prior art itself reflects an appropriate level and a need for testimony is not shown” (quoting *Litton Indus. Prods., Inc. v. Solid State Sys. Corp.*, 755 F.2d 158, 163 (Fed. Cir. 1985))).

B. Claim Construction

We interpret a claim “using the same claim construction standard that would be used to construe the claim in a civil action under 35 U.S.C. 282(b).” 37 C.F.R. § 42.100(b) (2019). Under this standard, we construe the claim “in accordance with the ordinary and customary meaning of such claim as understood by one of ordinary skill in the art and the prosecution history pertaining to the patent.” *Id.*

Petitioner proposes claim construction for three terms under their plain and ordinary meaning. *See* Pet. 41–42. First, Petitioner asserts that the “POSA would have understood that the term ‘native’ in the phrase ‘native conformation’ in claims 1, 2, 10 and 11 refers to the fully intact and functional conformation of the protein.” *Id.* at 42 (citing Ex. 1002 ¶ 22). Second, Petitioner asserts that the “POSA would have understood the term ‘vial’ in claims 1–9 to refer to a small closed or closable vessel, especially for liquids.” *Id.* (citing Ex. 1031; Ex. 1002 ¶¶ 23, 190). Third, Petitioner

asserts that the “[t]he POSA would have understood the term ‘multimerizing component’ in claims 1 and 10 to refer to a protein moiety that joins two or more protein domains together to form a multimer, such as a dimer or trimer.” *Id.* (citing Ex. 1002 ¶ 24). Patent Owner does not challenge Petitioner’s proposed claim constructions. Prelim. Resp. 16.

For purposes of this Decision, however, we determine that no claim terms require express construction. *See Nidec Motor Corp. v. Zhongshan Broad Ocean Motor Co.*, 868 F.3d 1013, 1017 (Fed. Cir. 2017) (citing *Vivid Techs., Inc. v. Am. Sci. & Eng’g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999) (“[O]nly those terms need be construed that are in controversy, and only to the extent necessary to resolve the controversy.”)).

C. Asserted Anticipation of Claims 1–18 by Fraser

Petitioner contends that claims 1–18 are anticipated by Fraser. Pet. 42–53. Patent Owner disputes Petitioner’s contentions. Prelim. Resp. 16–44.

1. Principles of Law

To establish anticipation under 35 U.S.C. § 102, each and every element in a claim, arranged as recited in the claim, must be found in a single prior art reference. *Net MoneyIN, Inc. v. VeriSign, Inc.*, 545 F.3d 1359, 1369 (Fed. Cir. 2008); *Karsten Mfg. Corp. v. Cleveland Golf Co.*, 242 F.3d 1376, 1383 (Fed. Cir. 2001). Each element of the challenged claim must be found, either expressly or inherently, in the single prior art reference. *Verdegaal Bros., Inc. v. Union Oil Co. of Cal.*, 814 F.2d 628, 631 (Fed. Cir. 1987). When evaluating a prior art reference in the context of anticipation, the reference must be “considered together with the knowledge of one of ordinary skill in the pertinent art.” *In re Paulsen*, 30 F.3d 1475, 1480 (Fed. Cir. 1994) (citing *In re Samour*, 571 F.2d 559, 562 (CCPA

1978)). “[A] reference can anticipate a claim even if it ‘d[oes] not expressly spell out’ all the limitations arranged or combined as in the claim, if a person of skill in the art, reading the reference, would ‘at once envisage’ the claimed arrangement or combination.” *Kennametal, Inc. v. Ingersoll Cutting Tool Co.*, 780 F.3d 1376, 1381 (Fed. Cir. 2015) (quoting *In re Petering*, 301 F.2d 676, 681 (CCPA 1962)).

2. *Petitioner’s Position*

Petitioner contends that Fraser discloses a formulation comprising a VEGF antagonist, specifically VEGF Trap_{R1R2}. Pet. 43 (citing Ex. 1009, 1115; Ex. 1002 ¶ 90). According to Petitioner, VEGF Trap_{R1R2} is a fusion protein comprising Ig domain 2 of VEGF-R1, Ig domain 3 of VEGF-R2, and human Fc, a multimerizing component. *Id.* (citing Ex. 1009, 1115). Petitioner contends that Fraser further discloses that the formulation includes an organic co-solvent, i.e., Tween 20 (polysorbate 20); buffer, i.e., phosphate, citrate, and NaCl (pH 6.0); and a stabilizing agent, i.e., glycerol or sucrose. *Id.* at 44–45 (citing Ex. 1009, 1115; Ex. 1002 ¶¶ 73, 91–92). As to claim 1 specifically, Petitioner contends that “[t]he *Fraser* formulation was necessarily present in a ‘vial’ and a POSA reading *Fraser* would have understood this.” *Id.* at 48–50 (citing Ex. 1002 ¶¶ 104–113).

Petitioner notes that Fraser states that the VEGF Trap_{R1R2} formulation contained either 20% glycerol or 20% sucrose, but cites to Regeneron’s prosecution statements and lab notebooks as indicating that the Fraser formulation contained 20% sucrose. Pet. 45 (citing Ex. 1022, Exhibit C; Ex. 1023, 2). Petitioner also contends that a POSA would have understood that Fraser’s VEGF Trap_{R1R2} was produced in CHO cells. *Id.* Specifically, Petitioner contends that Fraser’s VEGF Trap_{R1R2} “‘was provided’ by Regeneron,” and Fraser references Holash to describe the properties of

VEGF Trap_{R1R2}. *Id.* (citing Ex. 1009, 1115). According to Petitioner, Holash discloses that VEGF Trap_{R1R2} was produced and purified from CHO cells. *Id.* (citing Ex. 1010, 11393–11394). Petitioner asserts that Fraser’s reference to VEGF Trap_{R1R2} being “provided” by Regeneron and the disclosure of Holash “would have informed a POSA that the VEGF Trap_{R1R2} in *Fraser* was produced in CHO cells.” *Id.* at 45–46 (citing Ex. 1002 ¶¶ 93–95). Similarly, Petitioner asserts that Wulff, the ’319 publication, and the ’309 publication also confirm that Fraser’s VEGF Trap_{R1R2} protein was produced in CHO cells. *See id.* at 46 (citing Ex. 1016, 2798; Ex. 1027 ¶ 26; Ex. 1029, Example 21; Ex. 1002 ¶¶ 93–95).

Petitioner acknowledges that Fraser does not disclose that at least 98% of VEGF Trap_{R1R2} in the formulation is present in native conformation after storage at 5° C for two months. *See* Pet. 46. However, Petitioner argues that “the stability of the *Fraser* formulation is the natural result of its ingredients.” *Id.* (citing Ex. 1002 ¶¶ 96–102). First, Petitioner contends that “[t]he fact that the *Fraser* formulation has the same ingredients as the claimed formulation is enough to establish a *prima facie* case of anticipation,” *Id.* at 46–47 (citing *In re Best*, 562 F.2d 1252, 1255 (CCPA 1977)). Second, Petitioner asserts that “[a]nother Regeneron publication, *Dix*, published after the priority date, disclosed that Regeneron conducted stability testing on the same formulation and found that greater than 99% of the aflibercept remained in native conformation as measured by SEC after storage for 2 months at 5 °C.” *Id.* at 47–48 (citing Ex. 1002 ¶¶ 96–102; Ex. 1021, 11:15–12:20, Table 9; Ex. 1002 ¶¶ 97, 100).

3. Patent Owner’s Position

Patent Owner raises two main arguments. First, Patent Owner contends that Petitioner has not shown that Fraser’s formulation meets the

“native conformation limitation.” *See* Prelim. Resp. 16–41. Second, Patent Owner contends that Petitioner has not shown that Fraser’s fusion protein was created in CHO cells. *See id.* at 41–44.

Patent Owner’s first argument seeks to distinguish Fraser’s VEGF Trap_{R1R2} from Dix’s VEGF trap protein (amino acid SEQ ID NO:4), so that Petitioner cannot rely on Dix’s stability data for inherency. *See* Prelim. Resp. 16–18; *see* Sur-Reply 1–3. Patent Owner argues that “Fraser and Wulff set forth the broad structural characteristics needed to qualify as a ‘VEGFTrap_{R1R2}’ or ‘R1R2,’ which is a genus of fusion proteins, not a single molecule.” Prelim. Resp. 19 (citing Ex. 2001 ¶¶ 39–43). Patent Owner also argues that the ’319 publication supports this contention by disclosing that two R1R2 fusion proteins, Flt1.D2.Flk1D3.FcΔC1(a) and VEGFR1R2-FcΔC1(a), “are distinct fusion proteins, with distinct amino acid sequences.” *Id.* at 20–25 (citing Ex. 1029, 21:16–17, 22:1–2, 51:5–12, 58:22–59:10, 61:2–8, 67:4–15, Figures 21A–21C, 24A–24C; Ex. 2001 ¶¶ 46–50, 53–61, 63–65).

According to Patent Owner, for the same reasons, the ’319 publication and the ’309 publication do not establish “that Fraser or Wulff used ‘VEGF-Trap_{R1R2}’ or similar terms to refer to—and only to—aflibercept.”¹³ Prelim. Resp. 35–37; *see* Sur-Reply 5. Finally, Patent Owner argues that Petitioner cannot use Patent Owner’s “post-priority statements” to show that Fraser’s VEGF Trap_{R1R2} is the same as Dix’s protein. *See* Prelim. Resp. 32–35.

¹³ In response to these arguments, Petitioner contends that the VEGF Trap_{R1R2} protein, disclosed by Fraser, Wulff, and Holash, and VEGFR1R2-FcΔC1(a), disclosed by the ’309 publication, all refer to the same protein, “aflibercept” and that Patent Owner has previously referred to VEGF Trap_{R1R2}, described in Holash, as aflibercept. *See* Reply 1–4; Pet. 14 n.1 (citing Ex. 1020, 2, 6–7; Ex. 1002 ¶ 64).

According to Patent Owner, their statement to the Office that “[t]he name of the active ingredient of EYLEA™ is aflibercept, also known as VEGF trap, VEGF-trap, VEGF Trap-Eye and VEGF-TRAP_{R1R2},” merely indicates that “aflibercept may sometimes be referred to by the name of the genus to which it belongs” *Id.* at 32–33. Patent Owner further argues, that as a matter of law, “Patent Owner’s post-priority date statements cannot be relied upon to ‘fill in’ missing disclosures in the prior art.” *Id.* at 34; *see* Sur-Reply 3–4 (citing *Endo Pharms. Sols., Inc. v. Custopharm, Inc.*, 894 F.3d 1374, 1383 (Fed. Cir. 2018) (“*Endo*”)).

Separately from arguing that Fraser does not disclose the same fusion protein as Dix, Patent Owner also argues that neither Fraser nor Wulff discloses the same formulation as Dix. *See* Prelim. Resp. 37–41. Patent Owner contends that “Fraser does not make clear that it used ‘20% sucrose’ as a stabilizer, as Dix did.” *Id.* Thus, Patent Owner contends that one cannot assume “that the data disclosed in Dix applies to the formulation used in Fraser when Petitioner fails to show that both references used the same formulation.” *Id.* Patent Owner further argues that Petitioner’s expert concedes that Fraser’s formulation and Dix’s formulation have different lot numbers, “suggesting that the proteins and/or formulations are *not* the same.” *Id.* at 28 (citing Ex. 1002 ¶ 101 n.6).

Patent Owner’s second main argument is that Petitioner fails to demonstrate that Fraser’s VEGF Trap_{R1R2} was necessarily created in CHO cells. *See* Prelim. Resp. 41–44. Patent Owner argues that Fraser’s reference to Holash does not indicate that the same VEGF Trap_{R1R2} from Holash was used by Fraser or that Holash’s host cell applies to Fraser but, rather, Holash is cited for other properties of VEGF Trap_{R1R2}. *See id.* at 41–43 (citing Pet. 45; Ex. 1009, 1115; Ex. 1017, 1393).

With regard to the disclosure of Wulff, Patent Owner argues that “[w]hether Wulff might cause a POSA to speculate that perhaps CHO cells were used to produce the Fraser protein is not relevant to whether Petitioner has shown that Fraser *anticipates* the challenged claims.” Prelim. Resp. 43–44. Accordingly, Patent Owner contends that “Petitioner thus has not met its burden to show that Fraser discloses that the particular VEGF Trap_{R1R2} protein used therein was produced in CHO cells.” *Id.* at 44.

4. Analysis

We first address Patent Owner’s argument that Petitioner has failed to show that Fraser discloses the same protein as in Dix (SEQ ID NO:4) because Dix refers to a specific protein while Fraser refers to a genus of proteins. Prelim. Resp. 18–37.

We agree with Petitioner that Fraser discloses VEGF Trap_{R1R2} as a specific protein molecule, describing it as “a recombinant, chimeric *protein*” that is “a *successor molecule*” to Patent Owner’s earlier VEGTrap_{A40}. Reply 1–2 (citing Ex. 1009, 1114–15). Fraser refers to the protein as “the VEGF Trap_{R1R2}” and reports its specific physical, pharmacokinetic, and pharmacodynamic properties. *Id.* at 2 (citing Ex. 1009, 1115). The ’309 publication also indicates that VEGF Trap_{R1R2} is a particular protein having a specific amino acid sequence. Ex. 1027 ¶ 5 (“In a specific and preferred embodiment, the VEGF trap is VEGFR1R2-FcΔC1(a) (also termed VEGF trap_{R1R2}) having the nucleotide sequence set forth in SEQ ID NO: 1 and the amino acid sequence set forth in SEQ ID NO: 2”).¹⁴

¹⁴ Petitioner represents that the amino acid sequence from the ’309 publication is the same as the one disclosed in Dix as well as other Regeneron publications. *See* Pet. 14–15, 24–25, 47–48 (citing Ex. 1002 ¶¶ 64, 65, 97; Ex. 1029, 12, 15, Fig. 24A–24C; Ex. 1028 ¶ 8. SEQ ID Nos. 3

We further agree with Petitioner that Wulff discloses “[t]he VEGF Trap_{R1R2} used in [its] experiments” as a single protein with a specific structure. Reply 2 (citing Ex. 1016, 2798) (alterations in original). Wulff discloses that “VEGF Trap_{R1R2}” was a “new compound” and “a recombinant chimeric protein” and that the “detailed molecular structure” of the protein “and how it was created” was described in the ’319 publication. Ex. 1016, 2797–98, 2798 n.1, 2804.

We are not persuaded by Patent Owner’s argument that the ’319 publication supports its assertion that the protein disclosed in Fraser is a genus of proteins because the ’319 publication discloses that two R1R2 fusion proteins, Flt1.D2.Flk1D3.FcΔC1(a) and VEGFR1R2-FcΔC1(a), “are distinct fusion proteins, with distinct amino acid sequences.” Prelim. Resp. 20–25. The ’319 publication refers to these two proteins as two “R1R2” proteins, not as two “VEGF Trap_{R1R2}” proteins. Patent Owner does not cite to any references in which the term, “VEGF Trap_{R1R2},” is used to refer to more than one protein. Thus, we find that, on the current record, Petitioner has sufficiently shown that the VEGF Trap_{R1R2} protein disclosed in Fraser is a specific protein having the same amino acid sequence as the protein disclosed in Dix.

We further find that Petitioner has shown that Fraser discloses the claimed formulation. On the current record, Petitioner sufficiently demonstrates that Fraser’s VEGF Trap_{R1R2} formulation includes an organic co-solvent, i.e., Tween 20 (polysorbate 20); buffer, i.e., phosphate, citrate,

and 4; Ex. 1019, 10:15–17, Figs. 24A–24C; Ex. 1019, 10:15–17, Figs. 24A–24C; Ex. 1020, 6–7; Ex. 1021, 11:15–12:20, Table 9). Patent Owner does not contest this representation.

and NaCl (pH 6.0); and a stabilizing agent, i.e., glycerol or sucrose.
Ex. 1009, 1115; Ex. 1002 ¶¶ 73, 91–92.

Patent Owner asserts that Petitioner has not shown that Fraser discloses the same formulation as Dix because “Fraser does not make clear that it used ‘20% sucrose’ as a stabilizer, as Dix did.” Prelim. Resp. 37–41. Fraser discloses that the formulation includes “either 20% glycerol or 20% sucrose.” Ex. 1009, 1115. Petitioner cites to lab notebook pages and statements made by Patent Owner during patent prosecution to show that Fraser used 20% glucose in its formulation. *See* Pet. 45 (citing Ex. 1023, 2). Specifically, during prosecution of Dix, Patent Owner submitted lab notebook pages showing the “actual lot and formulation used in Fraser,” which included “20% sucrose.” Ex. 1023, 2 (citing Ex. 1022, Exhibit C). Petitioner also cites to Wulff, which discloses use of a VEGF Trap_{R1R2} formulation including “20% (wt/vol) sucrose.” Pet. 28 (citing Ex. 1016, 2798).

Although Patent Owner’s statements during prosecution of Dix establish that the Fraser formulation did, in fact, include 20% sucrose, Patent Owner contends that the “post-priority date statements cannot be relied upon to ‘fill in’ missing disclosures in the prior art as a matter of law.” Prelim. Resp. 34 (citing *Endo*, 894 F.3d at 1378–83). We find the *Endo* case to be distinguishable. In *Endo*, the claims required a benzyl benzoate co-solvent to be present in a particular ratio with the solvent and the prior art did not even disclose the use of a co-solvent in the formulation. *Endo*, 894 F.3d at 1380–1383. The court found that the prior art disclosure was insufficient to show inherency of the benzyl benzoate in the claimed ratio despite it being later revealed that it was used in the formulation because the prior art, “failed to disclose that the composition’s vehicle formulation included

another, key ingredient, benzyl benzoate, let alone the ratio of benzyl benzoate to castor oil.” *Id.* at 1383. The court also found that “there was no evidence in the record that a skilled artisan could determine the non-disclosed vehicle formulation based on the reported pharmacokinetic performance profile, or that the non-disclosed vehicle formulation was necessarily a feature of the TU injection studied in the [prior art].” *Id.* The court concluded that, “[u]nder the circumstances of this case, the incomplete description of the TU injection composition elements denied skilled artisans from having access to that composition, thereby precluding use of the inherency doctrine to fill in disclosure about the product missing from the [prior art].” *Id.*

In this case, Fraser discloses a VEGF Trap_{R1R2} formulation that includes “either 20% glycerol or 20% sucrose.” Ex. 1009, 1115. In other words, Fraser provides an option of including 20% of two different possible stabilizing agents, in contrast to the prior art in *Endo*, which did not even disclose the use of a co-solvent (and included no disclosure of any co-solvent amount). As such, we find that, on the current record, one of ordinary skill in the art would be able to “at once envisage” a VEGF Trap_{R1R2} formulation with 20% sucrose. *See Kennametal*, 780 F.3d at 1381. As a result, the Fraser disclosure does not “den[y] skilled artisans from having access to that composition,” as was the case in *Endo*.

Because we find, on the current record, that Petitioner has sufficiently shown that the VEGF Trap_{R1R2} formulation in Fraser is the same as that in Dix, we also find that Petitioner can rely on Dix to show the stability of the protein. As argued by Petitioner, Dix shows that greater than 99% of VEGF Trap_{R1R2} remained in native conformation as measured by SEC after storage for 2 months at 5° C. Ex. 1002 ¶¶ 96–102; Ex. 1021, 11:15–12:20, Table 9.

We agree with Petitioner that, while Fraser does not disclose this stability information, as evidenced by the data in Dix, such stability is necessarily a natural result of the formulation ingredients. Pet. 46 (citing *Abbott Labs. v. Baxter Pharm. Prods., Inc.*, 471 F.3d 1363, 1367 (Fed. Cir. 2006) (holding that “[o]ur cases have consistently held that a reference may anticipate even when the relevant properties of the thing disclosed were not appreciated at the time.”).

We also find that Petitioner has sufficiently shown that Fraser discloses that the VEGF Trap_{R1R2} disclosed therein was produced in CHO cells, as required by the claims. Fraser discloses that VEGF Trap_{R1R2} “was provided” by Regeneron and cites to the Holash paper in discussing the properties of VEGF Trap_{R1R2}. Ex. 1009, 1115. The Holash paper (Reference 21 in Fraser) states that “[a]ll of the VEGF-Trap variants were produced and purified from Chinese hamster ovary cells.” Ex. 1010, 11394.¹⁵

We acknowledge Patent Owner’s argument that Fraser’s citation to Holash does not mean that Fraser necessarily used CHO cells because Fraser does not “say that the VEGF Trap_{R1R2} used by the Fraser authors is the same as any of the VEGF-Trap variants described in Holash” (Prelim. Resp. 41); however, on the current record, we are persuaded by the testimony of Dr. Tarantino that the “VEGFTrap_{R1R2} disclosed in *Fraser* was created in CHO cells, and a POSA would have known as much when reading the term

¹⁵ Wulff also discloses that VEGF Trap_{R1R2} was manufactured in CHO cells and explains that the ’319 publication describes “the detailed molecular structure” of VEGF Trap_{R1R2} “and how it was created.” Ex. 1016, 2798, 2798 n.1. The ’319 publication (and the ’309 publication) also confirm that VEGF Trap_{R1R2} was produced in CHO cells. Ex. 1027 ¶ 22; Ex. 1029, Example 21; Ex. 1002 ¶¶ 93–95.

‘VEGFTrap_{R1R2}’ in the context of the whole *Fraser* article.” Ex. 1002 ¶ 93. As discussed above, Fraser refers to a particular protein, VEGF Trap_{R1R2}, and cites to a Regeneron publication (Holash) as describing the properties of this protein. Ex. 1009, 1115. Fraser then states that VEGF Trap_{R1R2} was provided by Regeneron to conduct the experiments described therein. *Id.* Based on this disclosure in Fraser, on the current record, we credit the currently unrebutted testimony of Dr. Tarantino that “[t]he reference by *Fraser* to VEGFTrap_{R1R2} being “provided” by Regeneron and directing the reader to *Holash* for a description of the protein would have informed the POSA that the VEGFTrap_{R1R2} in *Fraser* was made in CHO cells.” Ex. 1002 ¶ 94.

Patent Owner does not contest that Fraser discloses the other limitations of claims 1 and 10 and, on the current record, we find that Fraser does disclose these limitations. Accordingly, on the current record, Petitioner has demonstrated a reasonable likelihood that the subject matter of claims 1 and 10 of the ’992 patent is anticipated by the disclosure of Fraser. Petitioner also presents evidence and arguments as to how Fraser anticipates dependent claims 2–9 and 11–18. Pet. 48–53. Other than the arguments discussed above, Patent Owner does not present additional arguments further addressing the patentability of these claims. We have reviewed Petitioner’s arguments and evidence regarding these claims and find that, on the current record, Petitioner has also demonstrated a reasonable likelihood that claims 2–9 and 11–18 of the ’992 patent are anticipated by the disclosure of Fraser.

D. Asserted Obviousness over Fraser, Holash, and Wulff, in view of the '319 Publication, the '309 Publication, McNally 2000, and FDA Guidance

Petitioner contends that claims 1–18 would have been obvious over the combination of Fraser, Holash, and Wulff, in view of the '319 Publication, the '309 Publication, McNally 2000, and FDA Guidance.

Pet. 53–67. Patent Owner disputes Petitioner's contentions. Prelim. Resp. 44–52.

1. Principles of Law

A claim is unpatentable under 35 U.S.C. § 103 if the differences between the subject matter sought to be patented and the prior art are such that the subject matter, as a whole, would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. *See KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007). The question of obviousness is resolved on the basis of underlying factual determinations, including: (1) the scope and content of the prior art; (2) any differences between the claimed subject matter and the prior art; (3) the level of skill in the art; and (4) when in evidence, objective evidence of non-obviousness, i.e., secondary considerations. *See Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966).

2. Petitioner's Position

Petitioner argues that it would have been obvious for one of ordinary skill in the art to produce Fraser's VEGF Trap_{R1R2} in CHO cells and formulate the resulting VEGF Trap_{R1R2} into a stable formulation for therapeutic use having the claimed stability. *See* Pet. 54–63.

First, Petitioner contends that it would have been obvious to produce Fraser's VEGF Trap_{R1R2} in CHO cells because Holash and Wulff describe

producing the same fusion protein in CHO cells. *See* Pet. 56 (citing Ex. 1016, 2798; Ex. 1010, 11393–11394). Petitioner asserts that a POSA would “stick[] to a proven method that was already shown to have worked.” *Id.* at 56–57 (citing Ex. 1002 ¶¶ 143–145, 189; Ex. 1047, 12; Ex. 1017, 1396).

Second, Petitioner contends that it would have been obvious “to select an organic cosolvent, a buffer, and a stabilizing agent as excipients for a stable formulation” because “this was the *only* formulation of aflibercept that was published for *in vivo* use.” Pet. 58 (citing Ex. 1009, 1115; Ex. 1016, 2798; Ex. 1002 ¶¶ 146–147). Petitioner asserts that Fraser teaches “this formulation sufficiently stabilized the aflibercept so that it remained useable over a two-week period when stored at 4° C.” *Id.* at 58 (citing Ex. 1009, 1115).

Third, Petitioner argues that the native conformation limitation does not distinguish the claimed formulation from the prior art. *See* Pet. 59–63. Petitioner contends that “[m]erely claiming the results achieved by an obvious combination of ingredients does not distinguish that combination from the prior art.” *Id.* at 59 (citing *In re Best*, 562 F.2d at 1255). Petitioner further argues that storage stability is not critical to the formulation and instead, “[t]his limitation appears to only be the product of simply claiming the test results reported in the examples of the ’992 patent.” *Id.* Petitioner further argues that “a POSA would have been motivated to use the *Fraser* formulation [to] make a commercial aflibercept product that was as stable as possible.” *Id.* at 60. To do so, Petitioner argues that a POSA would have been motivated to minimize aggregation, because aggregates reduce the quality and potency of the product. *See id.* (citing Ex. 1002 ¶¶ 72–74, 154). Petitioner argues that “[a] POSA thus would have regarded the preservation

of at least 98% of the aflibercept in native conformation after storage for two months at 5° C as measured by SEC as being an obvious and desirable goal, and a level of 99% or greater to be even more desirable.” *Id.* at 61 (citing Ex. 1002 ¶¶ 153).

Fourth, Petitioner argues that a POSA would have made a stable formulation—defined by the native conformation limitation—by “simply doing the obvious thing and copying the *Fraser* formulation.” Pet. 61. Petitioner argues that “[a]s of 2006, formulators possessed a relatively high degree of skill in stabilizing protein therapeutics.” *Id.* Accordingly, Petitioner argues that “a POSA would have been able to make incremental adjustments to the concentrations of polysorbate 20, phosphate buffer, aflibercept, NaCl and pH, observed their impact on stability, and then made additional adjustments as necessary until they achieved maximum stability.” *Id.* (citing Ex. 1002 ¶¶ 153–159). Petitioner argues that McNally shows that it “would have been routine and well within ordinary skill” to design and execute experiments to determine the optimal value for each variable. *See id.* at 62 (citing Ex. 1002 ¶¶ 156–159; Ex. 1013, 156–157).

3. Patent Owner’s Position

Patent Owner argues that Petitioner may not rely on inherency to demonstrate obviousness, and that Petitioner has not shown a motivation to modify the references nor a reasonable expectation of success in doing so. *See* Prelim. Resp. 45–52. First, Patent Owner argues that “Petitioner advances the same inherency argument for its obviousness ground that it did for its anticipation ground, attempting to rely on the non-prior art Dix reference.” *Id.* at 46. However, Patent Owner argues that “[t]he data from Table 9 of Dix could not have informed the POSA’s understanding of the

stability of the Fraser formulation by the critical date because it did not exist as of the critical date” *Id.*

Second, Patent Owner argues that it would not have been obvious to seek a 98% native conformation. *See* Prelim. Resp. 47–49. Patent Owner argues that “it is not the case that formulators *always* attempt to get as close to 100% native conformation as possible—only driven by hindsight would a formulator set aside other constraints and priorities and seek single-mindedly to maximize native conformation.” *Id.* at 48 (citing Ex. 1006, 2, 4, 6; Ex. 2001 ¶¶ 25–27). According to Patent Owner, Petitioner’s references “describe formulations as ‘stable’ when a much lower fraction of the product—between 90% and 95%—was present in native conformation.” *Id.* (citing Ex. 1030, 8:31–33; Ex. 1026 ¶ 63; Ex. 1024 ¶ 36; Ex. 1025 ¶ 25). Patent Owner further argues that “native conformation below 98% was consistent with certain generally applicable standards.” *Id.* at 49 (citing Ex. 2014, 14; Ex. 2021, 5).

Third, Patent Owner argues that “Petitioner has not shown that, based on information available as of the priority date, a POSA would have reasonably expected the formulation of Fraser to exhibit at least 98% native conformation under the recited conditions.” Prelim. Resp. 50. Specifically, Patent Owner argues that Fraser’s disclosure of storing the compound at 4° C for 2 weeks “does not imply that the formulation would have maintained at least 98% native conformation after two months, or anything close to it.” *Id.* at 50 (citing Ex. 1009, 1115; Pet. 58). Notably, Patent Owner argues that usability at two weeks does not imply stability over two months as aggregates tend to form over time. *See id.* (citing Ex. 2020, 4; Ex. 1021, Examples 1–3). Finally, Patent Owner argues that “adequacy of a

formulation for a preclinical study does not imply adequacy for clinical trials and approval.” *Id.* at 50–51 (citing Ex. 1013, 147; Ex. 1006, 10).

4. *Analysis*

For the reasons explained above, we find that, on the current record, Petitioner has shown that Fraser discloses the limitations of the challenged claims of the ’992 patent. However, even, *assuming arguendo*, that Fraser does not disclose certain limitations, on the current record, we find that those limitations would have been obvious based on the disclosures in the other cited references. We are persuaded by Petitioner and Dr. Tarantino’s contentions that the “prior art would have given a POSA ample motivation of making a formulation” with VEGF Trap_{R1R2} based on studies published by Regeneron showing that VEGF Trap_{R1R2} “had the best *in vivo* pharmacokinetics and anti-VEGF activity of the VEGF-trap proteins Regeneron had been studying.” Pet. 55 (citing Ex. 1009; Ex. 1010; Ex. 1016; Ex. 1029, 10 (describing VEGFTrap_{R1R2} as having “improved pharmacokinetic properties”); Ex. 1002 ¶¶ 140–142).

Petitioner has also persuasively shown that “[t]he prior art also would have motivated a POSA to select an organic cosolvent, a buffer, and a stabilizing agent as excipients for a stable formulation of aflibercept” because Regeneron’s Fraser and Wulff publications disclosed “that it had formulated aflibercept for its *in vivo* studies using the organic co-solvent polysorbate 20, a buffer containing phosphate, and the stabilizing agent sucrose.” Pet. 58 (citing Ex. 1009, 1115; Ex. 1016, 2798; Ex. 1002 ¶¶ 146–147). We are further persuaded by the contention of Petitioner and Dr. Tarantino that this was the only formulation of aflibercept that was published for *in vivo* use as of the priority date, “which would have left the

POSA with only one clear starting point when making a formulation for such use.” *Id.* (citing Ex. 1002 ¶ 147).

We are similarly persuaded by Petitioner’s contention that a POSA would have been motivated to make VEGF Trap_{R1R2} in CHO cells because Regeneron’s Wulff and Holash publications disclosed that they had done so and a POSA would have done the same in order to reproduce the desirable performance of VEGF Trap_{R1R2} in those publications. Pet. 56 (citing Ex. 1002 ¶¶ 143–145, 189; Ex. 1010, 11393–11394; Ex. 1016, 2798; Ex. 1047, 12; Ex. 1017, 1396).

Patent Owner’s main argument is that a person of ordinary skill in the art would not have been motivated to produce a VEGF Trap_{R1R2} formulation in which 98% of the VEGF antagonist is present in native conformation following storage at 5° C for two months, nor would a POSA have had a reasonable expectation of success in doing so. Patent Owner also argues that Petitioner may not use Dix to demonstrate obviousness of the claimed stability requirements because they allege that Petitioner cannot rely on inherency in the context of its obviousness arguments. Prelim. Resp. 44–52. Patent Owner contends that *In re Best* is distinguishable because “Petitioner’s inherency argument is mistaken in the context of its anticipation argument, and Petitioner does not make a parallel single-reference obviousness argument [as in *Best*].” *Id.* at 47 n.1. Patent Owner also contends that “no party in *Best* attempted to show inherency with non-prior art data.” *Id.*

As explained above, based on the current record, we do not find Petitioner’s inherency arguments in the context of its anticipation argument to be “mistaken.” Also, while we invite the parties to further brief this issue, we are not persuaded that the reasoning in *In re Best* is limited to the context

of a single-reference obviousness argument as asserted by Patent Owner. We are similarly unpersuaded that *In re Best* does not apply to situations in which inherency is shown with non-prior art data.

On the current record, we find that Petitioner has persuasively shown that a person of ordinary skill in the art would have been able to achieve the claimed stability limitations by making the VEGF Trap_{R1R2} formulation disclosed in Fraser and Wulff. On the current record, we also agree with Petitioner that, if needed, one of skill in the art would have been able to optimize the Fraser formulation in view of the other cited references in order to achieve the claimed stability. *See E.I. DuPont de Nemours v. Synvina C.V.*, 904 F.3d 996, 1006 (Fed. Cir. 2018) (The fact that routine or trial-and-error experiments may be required to determine the optimum concentrations of ingredients in an otherwise old or obvious formulation does not make the optimized formulation inventive).

Thus, after carefully considering the arguments and evidence, we determine that, on this record, Petitioner has demonstrated a reasonable likelihood that the subject matter of claims 1 and 10 of the '992 patent would have been obvious over the disclosures of Fraser, Holash, and Wulff, in view of the '319 Publication, the '309 Publication, McNally 2000, and FDA Guidance. Petitioner also presents evidence and arguments as to how these references render obvious dependent claims 2–9 and 11–18 of the '992 patent. Pet. 63–66. Other than the arguments discussed above, Patent Owner does not present additional arguments further addressing the patentability of these claims. We have reviewed Petitioner's arguments and evidence regarding these claims and find that, on the current record, Petitioner has demonstrated a reasonable likelihood that the subject matter of claims 2–9 and 11–18 of the '992 patent is rendered obvious by the

disclosure of Fraser, Holash, and Wulff, in view of the '319 Publication, the '309 Publication, McNally 2000, and FDA Guidance.

V. CONCLUSION

For the forgoing reasons, Petitioner has demonstrated a reasonable likelihood that at least one challenged claim of the '992 patent is anticipated by and/or would have been obvious over the prior art of record.

Accordingly, we institute an *inter partes* review on claims 1–18 for all grounds set forth in the Petition.

VI. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that, pursuant to 35 U.S.C. § 314, an *inter partes* review is instituted on claims 1–18 for all grounds set forth in the Petition; and

FURTHER ORDERED that, pursuant to 35 U.S.C. § 314(c) and 37 C.F.R. § 42.4, *inter partes* review of the '992 patent shall commence on the entry date of this Order, and notice is hereby given of the institution of a trial.

IPR2023-00462
Patent 10,464,992 B2

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The United States Patent and Trademark Office
PATENT TRIAL AND APPEAL BOARD



A petition has been filed in Patent Number 10,464,992 B2, Application Number 16/159,269
on 8/18/23 (Date).

The Case Number is IPR2023-01312.
(IPR, CBM, PGR, DER #)

To view the documents filed in this petition, go to <https://ptab.uspto.gov>.

Use the Search PTAB tab and enter the Patent Number or the Trial or Case Number and select the Search button.

Questions regarding this notice should be directed to the Patent Trial and Appeal Board at 571-272-7822.

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

SAMSUNG BIOEPIS CO., LTD.,
PETITIONER,

v.

REGENERON PHARMACEUTICALS, INC.,
Patent Owner.

Case IPR2023-01312
Patent 10,464,992 B2

Mailed: August 30, 2023

Before KAREN I. SWEENEY, *Trial Paralegal*

NOTICE OF FILING DATE ACCORDED TO PETITION
AND
TIME FOR FILING PATENT OWNER PRELIMINARY RESPONSE

The petition for *inter partes* review filed in the above proceeding has been accorded the filing date of August 18, 2023.

Patent Owner may file a preliminary response to the petition no later than three months from the date of this notice. The preliminary response is limited to setting forth the reasons why the requested review should not be instituted. Patent Owner may also file an election to waive the preliminary response to expedite the proceeding. For more information, please consult

the Office Patent Trial Practice Guide, 77 Fed. Reg. 48756 (Aug. 14, 2012), which is available on the Board Web site at <http://www.uspto.gov/PTAB>.

Patent Owner is advised of the requirement to submit mandatory notice information under 37 C.F.R. § 42.8(a)(2) within 21 days of service of the petition. Mandatory notices include identifying any other judicial or administrative matter that would affect, or be affected by, a decision in the proceeding. 37 C.F.R. § 42.8(b)(2). Such administrative matters include requests for certificates of correction.

The parties are encouraged to use the heading on the first page of this Notice for all future filings in the proceeding.

The parties are advised that under 37 C.F.R. § 42.10(c), recognition of counsel *pro hac vice* requires a showing of good cause. The parties are authorized to file motions for *pro hac vice* admission under 37 C.F.R. § 42.10(c). Such motions shall be filed in accordance with the “Order -- Authorizing Motion *for Pro Hac Vice* Admission” in Case IPR2013-00639, Paper 7, a copy of which is available on the Board Web site under “Representative Orders, Decisions, and Notices.”

The parties are reminded that unless otherwise permitted by 37 C.F.R. § 42.6(b)(2), all filings in this proceeding must be made electronically in the Patent Trial Appeal Case Tracking System (P-TACTS), accessible from the Board Web site at <http://www.uspto.gov/PTAB>.

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The parties are directed to contact the Board within a month of this Order if there is a need to discuss proposed changes to this Scheduling Order or proposed motions that have not been authorized in this Order or other prior Order or Notice. *See* Consolidated Trial Practice Guide (“Trial Practice Guide”)^[1] at 9–10, 65 (guidance in preparing for a conference call); *see also* 84 Fed. Reg. 64,280 (Nov. 21, 2019). A request for an initial conference call shall include a list of proposed motions, if any.

The parties may request additional conference calls as needed. Any email requesting a conference call with the Board should: (a) copy all parties, (b) indicate generally the relief being requested or the subject matter of the conference call, (c) include multiple times when all parties are available, (d) state whether the opposing party opposes any relief requested, and (e) if opposed, either certify that the parties have met and conferred telephonically or in person in an attempt to reach agreement, or explain why such meet and confer did not occur. The email may not contain substantive argument and, unless otherwise authorized, may not include attachments. *See* Trial Practice Guide at 9–10. If practicable, in order to ensure emails are consistent with the above, the panel recommends that the parties send a single, joint email that includes items (a)–(e).

If there are any questions pertaining to this notice, please contact Karen I. Sweeney at 571-272-4673 or the Patent Trial and Appeal Board at 571-272-7822.

^[1] Available at <https://www.uspto.gov/TrialPracticeGuideConsolidated>.

IPR2023-01312
Patent 10,464,992 B2

PETITIONER:

Raymond N. Nimrod
Matthew A. Traupman
Landon A. Smith
QUINN EMANUEL URQUHART & SULLIVAN, LLP
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matthewtraupman@quinnemanuel.com
landonsmith@quinnemanuel.com

PATENT OWNER:

A&P – REGENERON
Attn: IP Docketing
601 Massachusetts Avenue, N.W.
Washington, DC 20001-3743

**NOTICE CONCERNING ALTERNATIVE DISPUTE RESOLUTION
(ADR)**

The Patent Trial and Appeal Board (PTAB) strongly encourages parties who are considering settlement to consider alternative dispute resolution as a means of settling the issues that may be raised in an AIA trial proceeding. Many AIA trials are settled prior to a Final Written Decision. Those considering settlement may wish to consider alternative dispute resolution techniques early in a proceeding to produce a quicker, mutually agreeable resolution of a dispute or to at least narrow the scope of matters in dispute. Alternative dispute resolution has the potential to save parties time and money.

Many non-profit organizations, both inside and outside the intellectual property field, offer alternative dispute resolution services. Listed below are the names and addresses of several such organizations. The listings are provided for the convenience of parties involved in cases before the PTAB; the PTAB does not sponsor or endorse any particular organization's alternative dispute resolution services. In addition, consideration may be given to utilizing independent alternative dispute resolution firms. Such firms may be located through a standard keyword Internet search.

CPR INSTITUTE FOR DISPUTE RESOLUTION	AMERICAN INTELLECTUAL PROPERTY LAW ASSOCIATION (AIPLA)	AMERICAN ARBITRATION ASSOCIATION (AAA)	WORLD INTELLECTUAL PROPERTY ORGANIZATION (WIPO)	AMERICAN BAR ASSOCIATION (ABA)
Telephone: (212) 949-6490	Telephone: (703) 415-0780	Telephone: (212) 484-3266	Telephone: 41 22 338 9111	Telephone : (202) 662-1000
Fax: (212) 949-8859	Fax: (703) 415-0786	Fax: (212) 307-4387	Fax: 41 22 733 5428	N/A
575 Lexington Ave	241 18th Street, South, Suite 700	140 West 51st Street	34, chemin des Colombettes	1050 Connecticut Ave, NW
New York, NY 10022	Arlington, VA 22202	New York, NY 10020	CH-1211 Geneva 20, Switzerland	Washington D.C. 20036
www.cpradr.org	www.aipla.org	www.adr.org	www.wipo.int	www.americanbar.org

If parties to an AIA trial proceeding consider using alternative dispute resolution, the PTAB would like to know whether the parties ultimately decided to engage in alternative dispute resolution and the reasons why or why not. If the parties actually engage in alternative dispute resolution, the PTAB would be interested to learn what mechanism (e.g., arbitration,

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PTAB_ADR_Comments@uspto.gov

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

SAMSUNG BIOEPIS CO., LTD.,
PETITIONER,

v.

REGENERON PHARMACEUTICALS, INC.,
Patent Owner.

Case IPR2023-01312
Patent 10,464,992 B2

Mailed: August 30, 2023

Before KAREN I. SWEENEY, *Trial Paralegal*

NOTICE OF FILING DATE ACCORDED TO PETITION
AND
TIME FOR FILING PATENT OWNER PRELIMINARY RESPONSE

The petition for *inter partes* review filed in the above proceeding has been accorded the filing date of August 18, 2023.

Patent Owner may file a preliminary response to the petition no later than three months from the date of this notice. The preliminary response is limited to setting forth the reasons why the requested review should not be instituted. Patent Owner may also file an election to waive the preliminary response to expedite the proceeding. For more information, please consult

the Office Patent Trial Practice Guide, 77 Fed. Reg. 48756 (Aug. 14, 2012), which is available on the Board Web site at <http://www.uspto.gov/PTAB>.

Patent Owner is advised of the requirement to submit mandatory notice information under 37 C.F.R. § 42.8(a)(2) within 21 days of service of the petition. Mandatory notices include identifying any other judicial or administrative matter that would affect, or be affected by, a decision in the proceeding. 37 C.F.R. § 42.8(b)(2). Such administrative matters include requests for certificates of correction.

The parties are encouraged to use the heading on the first page of this Notice for all future filings in the proceeding.

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IPR2023-01312
Patent 10,464,992 B2

PETITIONER:

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Landon A. Smith
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matthewtraupman@quinnemanuel.com
landonsmith@quinnemanuel.com

PATENT OWNER:

A&P – REGENERON
Attn: IP Docketing
601 Massachusetts Avenue, N.W.
Washington, DC 20001-3743

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(ADR)**

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Fax: (212) 949-8859	Fax: (703) 415-0786	Fax: (212) 307-4387	Fax: 41 22 733 5428	N/A
575 Lexington Ave New York, NY 10022	241 18th Street, South, Suite 700 Arlington, VA 22202	140 West 51st Street New York, NY 10020	34, chemin des Colombettes CH-1211 Geneva 20, Switzerland	1050 Connecticut Ave, NW Washington D.C. 20036
www.cpradr.org	www.aipla.org	www.adr.org	www.wipo.int	www.americanbar.org

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PTAB_ADR_Comments@uspto.gov

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

DISCLAIMER IN PATENT UNDER 37 CFR 1.321(a)

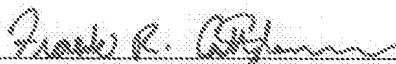
Name of Patentee Regeneron Pharmaceuticals, Inc.	Docket Number (Optional)
Patent Number 10,464,992	Date Patent Issued November 5, 2019

Title of Invention

VEGF ANTAGONIST FORMULATIONS SUITABLE FOR INTRAVITREAL ADMINISTRATIONI hereby disclaim the following complete claims in the above identified patent: 1-18Regeneron Pharmaceuticals, Inc. is disclaiming claims 1-18 in the '992 Patent for the sake of efficiency, as the patent is no longer needed.The extent of my interest in said patent is (if assignee of record, state liber and page, or reel and frame, where assignment is recorded): Assignee of record (reel/frame: 047899/0360)

The fee for this disclaimer is set forth in 37 CFR 1.20(d).

- ☐ Patentee claims small entity status. See 37 CFR 1.27.
- ☐ Small entity status has already been established in this case, and is still proper.
- ☐ A check in the amount of the fee is enclosed.
- ☐ Payment by credit card. Form PTO-2038 is attached.
- ☒ The Director is hereby authorized to charge any fees which may be required or credit any overpayment to Deposit Account No. 50-2387.

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.Signed at TARRYTOWN, State of NEW YORK, this 17TH day of JANUARY, 2024.

Signature

50,437

Registration Number, if applicable

Frank Cottingham
VP, Associate General Counsel, Intellectual Property, Regeneron Pharmaceuticals, Inc.914-847-1116

Typed or printed name of patentee/ attorney or agent of record

Telephone Number

777 Old Saw Mill River Road

Address

Tarrytown, NY 10591-6707

City, State, Zip Code or Foreign Country as applicable

This collection of information is required by 37 CFR 1.321. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

If you need assistance in completing the form, call 1-800-PTO-9199 and select option 2.



UNITED STATES
PATENT AND TRADEMARK OFFICE

P.O. Box 1450
Alexandria, VA 22313 - 1450
www.uspto.gov

ELECTRONIC ACKNOWLEDGEMENT RECEIPT

APPLICATION #
16/159,269

RECEIPT DATE / TIME
01/17/2024 02:45:18 PM Z ET

ATTORNEY DOCKET #
P35063US10/1106854.00082

Title of Invention

VEGF ANTAGONIST FORMULATIONS SUITABLE FOR INTRAVITREAL ADMINISTRATION

Application Information

APPLICATION TYPE Utility - Nonprovisional Application
under 35 USC 111(a)

PATENT # 10464992

CONFIRMATION # 5813

FILED BY Natherine Ordanza

PATENT CENTER # 63982808

FILING DATE 10/12/2018

CUSTOMER # 191459

FIRST NAMED
INVENTOR Eric FURFINE

CORRESPONDENCE
ADDRESS -

AUTHORIZED BY Michael Lewis

Documents

TOTAL DOCUMENTS: 1

DOCUMENT	PAGES	DESCRIPTION	SIZE (KB)
P35063US10__SD.pdf	1	Statutory disclaimers per Manual of Patent Examining Procedure(MPEP) 1490.	355 KB

Digest

DOCUMENT	MESSAGE DIGEST(SHA-512)
P35063US10__SD.pdf	2E1BE737D31AE0FE1FCE23EA62B8A076041225E1B091332DF 48E0171830BBED9EF7696BF86EFF0F35B8491CE4693C2C7A1 FCE993E1DEAADD280C13EEF14FCA29

This Acknowledgement Receipt evidences receipt on the noted date by the USPTO of the indicated documents, characterized by the applicant, and including page counts, where applicable. It serves as evidence of receipt similar to a Post Card, as described in MPEP 503.

New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.



UNITED STATES
PATENT AND TRADEMARK OFFICE

P.O. Box 1450
Alexandria, VA 22313 - 1450
www.uspto.gov

ELECTRONIC PAYMENT RECEIPT

APPLICATION # 16/159,269	RECEIPT DATE / TIME 01/17/2024 02:45:18 PM Z ET	ATTORNEY DOCKET # P35063US10/1106854.00082
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Title of Invention

VEGF ANTAGONIST FORMULATIONS SUITABLE FOR INTRAVITREAL ADMINISTRATION

Application Information

APPLICATION TYPE	Utility - Nonprovisional Application under 35 USC 111(a)	PATENT #	10464992
CONFIRMATION #	5813	FILED BY	Natherine Ordanza
PATENT CENTER #	63982808	AUTHORIZED BY	Michael Lewis
CUSTOMER #	191459	FILING DATE	10/12/2018
CORRESPONDENCE ADDRESS	-	FIRST NAMED INVENTOR	Eric FURFINE

Payment Information

PAYMENT METHOD CARD / 0128	PAYMENT TRANSACTION ID E20241GE45467749	PAYMENT AUTHORIZED BY Michael Lewis
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FEE CODE	DESCRIPTION	ITEM PRICE(\$)	QUANTITY	ITEM TOTAL(\$)
1814	STATUTORY DISCLAIMER, INCLUDING TERMINAL DISCLAIMER	170.00	1	170.00
TOTAL AMOUNT:				\$170.00

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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

CELLTRION, INC. and SAMSUNG BIOEPSIS CO., LTD.,¹
Petitioner,

v.

REGENERON PHARMACEUTICALS, INC.,
Patent Owner.

IPR2023-00462
Patent 10,464,992 B2

Before JOHN G. NEW, SUSAN L. C. MITCHELL, and JAMIE T. WISZ,
Administrative Patent Judges.

WISZ, *Administrative Patent Judge.*

DECISION
Adverse Judgment After Institution of Trial
37 C.F.R. § 42.73(b)

¹ Samsung Bioepsis Co., Ltd. filed a motion for joinder and a petition in IPR2023-01312 and has been joined as a petitioner in this proceeding. *See* Paper 30.

On January 17, 2023, Celltrion, Inc. (“Celltrion”) filed a Petition (Paper 2, “Pet.”) requesting an *inter partes* review of claims 1–18 of U.S. Patent No. 10,464,992 (Ex. 1001, “the ’992 patent”). We instituted *inter partes* review under 35 U.S.C. § 314(a). Paper 11 (“Inst. Dec.”). We joined Samsung Bioepsis Co., Ltd. (“Samsung”) as a petitioner in this proceeding, and we refer to Celltrion and Samsung collectively as “Petitioner.” *See* Paper 30.

Regeneron Pharmaceuticals, Inc. (“Patent Owner”) notified the Board, by email dated January 17, 2024, that it had filed a statutory disclaimer disclaiming claims 1–18 of the ’992 patent. *See* Ex. 3003. Patent Owner also filed a copy of the statutory disclaimer in this proceeding. *See* Ex. 2104. With the Board’s authorization, Patent Owner then filed an Unopposed Motion to Terminate Proceeding on January 22, 2024 in view of the disclaimer. Paper 35 (“Motion”). The Motion indicates that Petitioner does not oppose the Motion to Terminate Proceeding, but seeks to have the Board treat it as a request for adverse judgment under 37 C.F.R. § 42.73(b).

Patent Owner has disclaimed all claims of the ’992 patent and paid the requisite fees. *See* Ex. 2104; *see also* 37 C.F.R. § 1.321 (setting forth requirements for statutory disclaimer). Under 37 C.F.R. § 42.73(b), “[a]ctions construed to be a request for adverse judgment include . . . (2) [c]ancellation or disclaimer of a claim such that the party has no remaining claim in the trial.” Because Patent Owner has disclaimed all claims of the ’992 patent, we construe this disclaimer as a request for adverse judgment, and we enter adverse judgment against the Patent Owner with respect to claims 1–18 of the ’992 patent.

IPR2023-00462
Patent 10,464,992 B2

Accordingly, it is

ORDERED that judgment is entered under 37 C.F.R. § 42.73(b)
against Patent Owner with respect to claims 1–18 of U.S. Patent
No. 10,464,992 B2; and

FURTHER ORDERED that this proceeding is terminated.

IPR2023-00462
Patent 10,464,992 B2

FOR PETITIONER:

Lora Green
Yahn Lin Chu
GEMINI LAW LLP
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FOR PATENT OWNER:

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UNITED STATES PATENT AND TRADEMARK OFFICE

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Before JOHN G. NEW, SUSAN L. C. MITCHELL, and JAMIE T. WISZ,
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IPR2023-00462
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